The Promise and Peril of Using the Law to Promote Ethical Outcomes in Health and Healthcare

THE PROMISE AND PERIL OF USING THE LAW TO PROMOTE ETHICAL OUTCOMES IN HEALTH AND HEALTHCARE

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ABSTRACT

NOTA: NOT A GOOD ACT FOR TISSUES TO FOLLOW

The National Organ Transplant Act of 1984 (NOTA) articulates the U.S. federal policy for organ transplantation. It seeks to ensure equitable allocation of donor organs and strives to increase the number of organs available for transplant. A trio of ethical concerns—commodification, exploitation, and coercion—motivated passage of NOTA broadly and the prohibition on organ sales in particular. Notably, NOTA *does not* distinguish between organs and tissues, a devastating oversight given the differences between the two, which include: who can donate; when donation can occur; how donated items are procured, processed, and stored; who receives the donated item and why; and government oversight. Tissues are not like organs in the ways that made NOTA an appropriate legislative solution to commodification, exploitation, and coercion. Rather, NOTA failed to address tissue-specific concerns both ethical and practical in nature. Thus, there is an acute need to develop tissue-specific legislation that enhances informed consent to protect donor autonomy; sets a schedule of payments for donors and intermediaries to promote distributive justice; and improves tracking of donated tissues to address patient safety concerns.

REGULATORY UNCERTAINTY, CONCEPTUAL CONFUSION, AND A PATH FORWARD ON OFFERS OF PAYMENT TO RESEARCH PARTICIPANTS

The practice of offering payment to individuals in exchange for their participation in clinical research is widespread and longstanding. Nevertheless, such payment remains the source of substantial debate, in particular about whether or the extent to which offers of payment coerce and/or unduly induce individuals to participate. Yet, the various laws, regulations, and ethical guidelines that govern the conduct of human subjects research offer relatively little in the way of specific guidance regarding what makes a payment offer ethically acceptable. This paper systematically examines the legal and ethical dimensions of offering payment to research participants. It argues that concerns about offers of payment to research participants can be attributed to the misguided view that such offers ought to be treated differently than offers of payment in other contexts, a form of "research exceptionalism." We show that rejection of research exceptionalism with respect to payment helps settle open debates about both how best to define coercion and undue influence, and how to understand the relation between these concepts and offers of payment. We argue for adoption of our preferred definitions, ideally by regulatory authorities, and against the conventional conservatism toward payment of research participants. Instead, we draw attention to the rarely asked, even radical, question: are research participants paid *enough*? We conclude by arguing that we ought to change the default to favor, rather than encourage suspicion of, offers of payment to research participants.

EBOLA & FDA: REVIEWING THE RESPONSE TO FIND LESSONS FOR THE FUTURE

In 2014, West Africa confronted the most severe outbreak of Ebola virus disease (EVD) in history. At the onset of the outbreak—as now—there were no therapies approved by the U.S. Food and Drug Administration (FDA) for prevention of, post-exposure prophylaxis against, or treatment of EVD. As a result, the outbreak spurred interest in developing novel treatments and vaccines; sparked calls to use experimental interventions in the field; and highlighted challenges to the standard approach to FDA approval of new drugs. Although the outbreak was geographically centered in West Africa, it brought to the fore issues of food and drug law and showcased FDA's global role in drug development, approval, and access. FDA's response to EVD highlights the panoply of Agency powers and demonstrates the flexibility of FDA's regulatory framework. This paper evaluates the strengths and weaknesses of FDA's response and makes policy recommendations regarding how FDA should respond to new and re-emerging public health threats going forward. The current pandemic of Zika virus infection is but one example of an emerging health threat that will require FDA involvement in order to achieve a successful response.

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NOTA: NOT A GOOD ACT FOR TISSUES TO FOLLOW

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If you have agreed to be an organ donor, you have likely also agreed to be a tissue donor,[1] as the laws in every state define the word "organ" to include both organs and tissues.[2] While 94.9% of the American public supports or strongly supports organ donation,[3] tissue donation is neither as well known nor as well understood.[4] To the

[1] Joseph Shapiro, *Am I A Tissue Donor, Too?*, NATIONAL PUBLIC RADIO, July 18, 2012, http://www.npr.org/2012/07/18/156968033/am-i-a-tissue-donor-too ("Lucinda Babers, the director of the D.C. Department of Motor Vehicles, explains that in Washington – and this is the way it works in almost every state – when you obtain a driver's license, or renew it, you're given a choice to donate or not donate. The box says: "I want to donate my organs and tissue.""); *see also* Laura A. Siminoff, Heather M. Traino, & Nahida Gordon, *Determinants of Family Consent to Tissue Donation*, 69 J. OF TRAUMA 956, 956 (2010) ("Nearly a quarter of family members interviewed were . . . unaware that a signed donor card was, in effect, an agreement to donate tissues and corneas as well as organs."); Andrew Conte & Luis Fábregas, *Gift of Life Worth Millions to Donation Organizations*, TRIBLIVE, August 21, 2013, http://triblive.com/news/allegheny/4408091-74/organ-organizations-procurement#axzz3TdNEjy5t (People who become tissue donors automatically agree to give tissue in all but three states: Nebraska, North Carolina, and Wisconsin.).

[2] WASHINGTON REGIONAL TRANSPLANT COMMUNITY, *Tissue Donation*, http://www.beadonor.org/donation-facts/tissue-donation (last visited Feb. 19, 2016).

[3] U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS), HEALTH RESOURCES & SERVICES ADMINISTRATION (HRSA), 2012 NATIONAL SURVEY OF ORGAN DONATION ATTITUDES AND BEHAVIORS, at 13–14. In 2012, 60.1% of those surveyed said they had granted permission for donation on their driver's license. *Id.* at 18.

[4] Siminoff, Traino, & Gordon, *supra* note 1, at 956 ("A survey of families who donated tissues indicated only one-half distinguished tissue donation from organ donation. Moreover, the public is generally unaware of the details of tissue donation, such as the preparation and distribution process, which can involve for-profit companies.") (internal citations omitted); *see also* Shannon L. Sander & Barbara Kopp Miller, *Public Knowledge and Attitudes Regarding Organ and Tissue Donation: An Analysis of the Northwest Ohio Community*, 58 PATIENT EDUCATION AND COUNSELING 154, 157 (2005); THE BLOOD AND TISSUE CENTER OF CENTRAL TEXAS, *Tissue Donation FAQs*, http://www.inyourhands.org/tissue-center/learn-more/tissue-donation-faq/ ("Most people have heard of organ donation, but tissue donation is not as commonly discussed.").
Tissue donation did receive heightened scrutiny in 2015 after an anti-abortion group, the Center for Medical Progress, accused Planned Parenthood of profiting from a fetal tissue donation program, a charge that Planned Parenthood denied. Denise Grady & Nicholas St. Fleur*, Fetal Tissue from Abortions for Research is Traded in a Gray Zone*, NEW YORK TIMES, http://www.nytimes.com/2015/07/28/health/fetal-tissue-from-abortions-for-research-is-traded-in-a-gray-zone.html?_r=0; Washington Post Editorial Board, Planned Parenthood has Been Absolved. The GOP Should Give Up Its Crusade, Washington Post, https://www.washingtonpost.com/opinions/planned-parenthood-has-been-absolved-the-gop-should-give-up-its-crusade/2016/01/26/49803df4-c462-11e5-a4aa-f25866ba0dc6_story.html (last visited Feb. 19, 2016). While this drew attention to tissue donation, debate over fetal tissue clearly implicates the controversy surrounding abortion, which is beyond the scope of this paper.

contrary, the public "lacks basic knowledge of the differences between organ and tissue donation."[5]

Tissues one can donate after death include tendons, ligaments, skin, bones, heart valves, and corneas.[6] After donation, these tissues can be used in a variety of ways—some life saving, some life enhancing, and some more appropriately characterized as frivolous. Skin can be used, for example, in the treatment of burn victims, veins in heart bypass operations, and bone in spinal fusion surgery.[7] Yet, donated tissue might also be "used for . . . elective plastic surgery, like a penis enlargement procedure,"[8] lip plumping, or wrinkle smoothing.[9] The differences between organ and tissue donation are remarkably wide-ranging and encompass who can donate; when donation can occur; how the donated items are procured, processed, and stored; who receives the transplant; why they receive it; and how donation and transplantation are regulated.

Significantly, the public's lack of basic knowledge about the differences between organ and tissue donation finds its parallel in the governing federal legislation, the National

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[5] Siminoff, Traino, & Gordon, *supra* note 1, at 962.

[6] HHS, *What Can Be Donated*, http://www.organdonor.gov/about/donated.html.

[7] J. Randall Boyer, *Gifts of the Heart . . . and Other Tissues: Legalizing the Sale of Human Organs and Tissues*, BYU L REV. 313, 331 (2012); *see also* MUSCULOSKELETAL TRANSPLANT FOUNDATION (MTF), *Donation FAQs*, http://www.mtf.org/donor_faq.html ("Long bones may be used to replace those invaded by cancer. . . . Smaller sections of bone are used to strengthen areas of a deformed spine and to fill areas where bone has been lost due to conditions that have damaged existing bone. Damaged tendons and ligaments may be reconstructed as well, thus strengthening the joint and assisting the patient in walking or running. Skin can be life-saving for critically burned patients. It is also used for hernia repair, pelvic floor reconstruction, and for breast reconstruction following mastectomy. Heart valves are used to replace damaged heart valves. Saphenous and femoral veins from the legs are used in cardiac bypass surgery for patients who have suffered cardiovascular (heart) disease.").

[8] Shapiro, *supra* note 1.

[9] *See* Kate Wilson, Vlad Lavrov, Martina Keller, Thomas Maier, & Gerard Ryle, *Human Corpses are Prize in Global Drive for Profits*, THE INTERNATIONAL CONSORTIUM OF INVESTIGATIONAL JOURNALISTS, http://www.icij.org/human-corpses-are-prize-global-drive-profits (2012).

Organ Transplant Act[10] (NOTA), which fails to differentiate between tissues and organs and instead treats them as if they were the same. NOTA seeks to promote the socially valuable use of donated organs in transplantation as well as to resolve deep ethical concerns—namely commodification, coercion, and exploitation—that are raised by transactions involving the human body or parts thereof. To this end, one of NOTA's central provisions bans the exchange of organs for "valuable consideration." Yet, because NOTA fails to adequately differentiate organs from tissues, it fails to resolve satisfactorily these same ethical concerns insofar as they arise in connection with tissues.

This article contributes to the literature by systematically describing the ways in which transplantable tissues and organs differ from one another and articulating the normative implications of these differences for policy. I argue that although the ethical concerns that motivated the passage of NOTA in 1984 may remain relevant to organs, those concerns do not arise in the same way in connection with tissues.[11] Tissues demand their own tailored response. Therefore, I propose that NOTA should no longer be applied to

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[10] P.L. 98-507. Passed in 1984, NOTA was Congress's first attempt regulate the growing practice of organ donation and transplantation. Debra Budiani-Saberi & Deborah M. Golden, *Advancing Organ Donation Without Commercialization: Maintaining the Integrity of the National Organ Transplant Act*, Issue Brief, American Constitutional Society (2009). NOTA's central feature is the provision that bans the buying and selling of organs. The persistent shortage of organs is often attributed to the requirement that organs be donated altruistically. *E.g.*, Sally L. Satel, *Why People Don't Donate Their Kidneys*, THE NEW YORK TIMES May 3, 2014 ("The problem lies in the requirement that all organs be given altruistically . . . ."); *see generally*, Lloyd R. Cohen, *Increasing The Supply Of Transplant Organs: The Virtues Of A Futures Market*, 58 GEO. WASH. L. REV. 1, 11-15 (1989); Henry Hansmann, *The Economics and Ethics of Markets for Human Organs*, 14 J. HEALTH POL. POL'Y & L. 57, 71 (1989).

[11] The tissue industry has evolved significantly in the three decades since NOTA was passed. C*f.* Robert A. Katz, *The Re-Gift of Life: Can Charity Law Prevent For-Profit Firms from Exploiting Donated Tissue and Nonprofit Tissue Banks?*, 55 DEPAUL LAW REVIEW 943, 951–971 (2006); *see also* Julia D. Mahoney, *The Market for Human Tissue*, 86 VA. L. REV. 163, 171 (2000) ("Over the past several decades, however, a revolution in scientific knowledge and medical technology has dramatically increased the potential economic value of the human body."); Marc O. Williams, *The Regulation of Human Tissue in the United States: A Regulatory and Legislative Analysis*, 52 FOOD AND DRUG L.J. 409, 409 (1997) ("In the five decades that have elapsed since the inception of human tissue banking and transplantation in the United States, both the medical and economic significance of this technology have ballooned.").

tissues. Instead, I favor limiting NOTA to transplantable organs and creating a new regulatory scheme fitted to cadaveric tissues.

This article proceeds as follows: Part I describes the legal background to organ and tissue donation and outlines the legislative history of NOTA, which gives particular insight to the ethical concerns that motivated its passage. Part II catalogs the five key differences between organs and tissues. Part III argues that tissues are not like organs in the ways that made NOTA an appropriate regulatory scheme for vital organs. Part IV contends that tissues are sufficiently distinct from organs that they should be severed from NOTA and governed by a separate tissue-specific act that emphasizes informed consent, sets a schedule for reasonable profits for the tissue industry, permits the sale of tissues by donors, and requires improved tracking of products made from human tissue.

I. Historical and Legal Background to NOTA

The first skin transplant was performed in 1869 and the first cornea transplant in 1906.[12] The first successful kidney transplant was performed in 1954, when a living donor gave a kidney to his identical twin.[13] The first successful heart transplant was performed in

[12] HHS, *Timeline of Historical Events: Significant Milestones in Organ Donation and* Transplantation, http://www.organdonor.gov/legislation/timeline.html.

The U.S. Navy. Established the first tissue bank in 1949. Laura A. Buck, *Regulating Human Tissue Banks*, 20 ST. THOMAS L. REV. 121, 124 (2007). That bank remained the primary tissue bank in the United States for the next three decades. *Id.* Dr. George Hyatt, founder of the Navy's tissue bank, pioneered many techniques still used today, "including freeze-drying tissue for long-term storage, screening [of] donors for [transmittable] disease, . . . obtaining informed consent for donation, and the concept of an independent, free-standing tissue bank that functioned outside of an individual medical center." *Id.* With time, tissue banks were established to serve the needs of local communities; as the market for human tissue expanded, tissue banks began distributing outside of their communities. *Id.* The 1990s saw significant expansion of the tissue industry. *Id.*

[13] Dr. Joseph E. Murray transplanted a healthy kidney from Ronald Herrick to his identical twin, Richard, who had end-stage kidney failure; Richard survived for more than eight years without the use of

1967.[14] It was not until 1983, however, when the U.S. Food and Drug Administration (FDA) approved the immunosuppressant drug cyclosporine, which prevents transplant rejection, that widespread organ transplantation between unrelated individuals became possible.[15] As a result of the approval of cyclosporine, organ transplantation became a highly publicized issue in the early 1980s: stories of the miracles of organ transplantation were juxtaposed with individuals' desperate pleas for organ donations because no centralized transplantation organization existed.[16] People expressed frustration that, although transplantation was becoming a realistic clinical option for an increasing number of patients, "[a]ccess to transplant surgery depended on factors far removed from technical considerations, and many of these considerations seemed needlessly unfair to individual patients."[17]

In light of technological progression, it became necessary to establish legal and ethical boundaries for donation and transplantation. While state legislation predated

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immunosuppressive drugs. Kelly Ann Keller, *The Bed of Life: A Discussion of Organ Donation, Its Legal and Scientific History, and A Recommended "Opt-Out" Solution to Organ Scarcity*, 32 STETSON L. REV. 855, 865–866 (2003). Because this was a transplant between identical twins, it did not provide insights into how transplanted organs from an unrelated donor could survive in a recipient's body. *Id.* at 866. Most subsequent transplants failed due to rejection by the recipient's immune system until the discovery of cyclosporine. *Id.* at 866–867.

[14] *See generally* DONALD MCRAE, EVERY SECOND COUNTS: THE RACE TO TRANSPLANT THE FIRST HUMAN HEART (2006).

[15] *See* N.R. Banner & M.H. Yacoub, *Cyclosporine in Thoracic Organ Transplantation*, 36 TRANSPLANTATION PROCEEDINGS S302, S302 (2004) ("The discovery of cyclosporine proved to be a breakthrough that helped transform the status of both heart and lung transplantation from experimental to established therapeutic procedures."). Cyclosporine is an immunosuppressive agent that controls rejection. *Id.* at S302–S303.

[16] Gail L. Daubert, *Politics, Policies, and Problems with Organ Transplantation: Government Regulation Needed to Ration Organs Equitably*, 50 ADMIN. L. REV. 459, 462 (1998). Daubert describes how hospitals competed for organs in some regions of the country, while no transplant centers existed in other areas of the country. *Id.*

[17] Jed A. Gross, *E Pluribus UNOS: The National Organ Transplant Act and Its Postoperative Complications*, 8 YALE J. HEALTH POL'Y, L. & ETHICS 145, 175 (2008).

federal legislation, both sought to increase the number of donors and to ensure that the transplantation system retained its altruistic character.[18]

A. Uniform Anatomical Gift Act

By the mid-1960s, forty-two states had adopted some form of organ donation statute allowing a person to bequeath organs for transplantation.[19] These laws did little more than restate common law and were criticized for being both inadequate and confusing.[20] In 1965, the National Conference of Commissioners of Uniform State Laws responded to these critiques by drafting the Uniform Anatomical Gift Act (UAGA).[21] The Commissioners approved the UAGA in 1968, and by 1972, all fifty states and the District of Columbia had enacted it in one form or another.[22] The UAGA's purpose was to balance the rights and interests of the deceased and their families with society's need for post-mortem organ donations.[23] Notably, the 1968 UAGA did *not* ban the sale of organs. The UAGA's

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[18] Keller, *supra* note 13, at 879–880, 881–882.

[19] Theodore Silver, *The Case for a Post-Mortem Organ Draft and A Proposed Model Organ Draft Act*, 68 B.U. L. REV. 681, 692 (1988).

[20] *Id*. Additionally, they failed to address interstate transactions, which added to the confusion. *Id.* at 692–693. *See generally*, Richard J. Sideman & Eric D. Rosenfeld, *Legal Aspects of Tissue Donation from Cadavers*, 21 SYRACUSE L. REV. 825 (1970) (examining the impact of common law prohibitions against testamentary disposition of human organs).

[21] Silver, *supra* note 19, at 693.

[22] *Id.* at 693.

[23] The 1968 UAGA identified five competing interests in the transplant context: (1) the deceased's wishes during his or her lifetime; (2) the wishes of the deceased's next of kin; (3) the state's interest in performing autopsies to determine the cause of death in a crime; (4) the "need of autopsy to determine the cause of death when private legal rights are dependent upon such a cause;" and (5) the society's need for "bodies, tissues, and organs for medical education, research, therapy, and transplantation." Unif. Anatomical Gift Act of 1968 prefatory n., 8A U.L.A. 64. *See also* Keller, *supra* note 13, at 882–883 (discussing how the UAGA balances these competing interests).

Drafting Chair suggested that the question of compensation "should be left to the decency of human beings."[24] Moreover, the drafters did not expect compensation to become a major problem and felt crafting a prohibition on compensation would "not be easy."[25]

The UAGA was amended in 1987 with an eye toward further increasing organ donations and addressing gaps in the 1968 UAGA.[26] Among the notable changes, the 1987 UAGA expressly prohibited the purchase and sale of organs.[27] A bare majority of states has adopted the amended UAGA with the specific prohibitions on sales.[28]

B. The National Organ Transplant Act

NOTA, which passed in 1984 with little debate and bipartisan support,[29] is the controlling federal law.[30] Prior to NOTA's enactment, regulation of organ donation and

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[24] Quoted in I.G. Cohen, *Can the Government Ban Organ Sale? Recent Court Challenges and the Future of U.S. Law on Selling Human Organs and Other Tissue*, 12 AM. J. TRANSPLANTATION 1983, 1983 (2012).

[25] *Id.*

[26] Ann McIntosh, *Regulating the "Gift of Life"—The 1987 Uniform Anatomical Gift Act*, 65 WASH. L. REV. 171, 175–176 (1990). The newer version of the UAGA simplified the process of becoming an organ donor by allowing a driver's license to evidence the intent to make an anatomical gift; mandated routine inquiry about donation; codified NOTA's prohibition of the sale of organs; and implemented a limited system of presumed consent to organ donation. Sean R. Fitzgibbons, *Cadaveric Organ Donation and Consent; A Comparative Analysis of the United States, Japan, Singapore, and China*, 6 ILSA J. Intl. & Comp. L. 73, 81-83 (1999).

[27] Unif. Anatomical Gift Act (1987) § 10.

[28] Cohen, *supra* note 24, at 1984.

Almost all states have excluded from prohibited sales human by-products such as blood, blood products, hair, in vitro preparations of human cells, sperm, ovum, and other tissues that are readily renewable by the human body. Gloria J. Banks, *Legal & Ethical Safeguards: Protection of Society's Most Vulnerable Participants in A Commercialized Organ Transplantation* System, 21 AM. J.L. & MED. 45, 73 (1995). Commerce in regenerative tissue is "viewed by state law as the provision of a service instead of the sale of a good because such tissue is considered incidental to the provision of medical services." *Id.* at 73.

[29] Donald Joralemon, *Shifting Ethics: Debating the Incentive Question in Organ Transplantation*, 27 J. MED. ETHICS 30, 30 (2001) ("The congressional hearings produced Public Law 98-507, "The National

transplantation had been exclusively a matter of state law.[31] The objective of NOTA was to articulate a national policy for organ transplantation, to ensure equitable allocation of donor organs, and to increase the number of organs available for transplant.[32]

1. NOTA's Key Provisions

> Under the Act, a "human organ" includes:
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> the human (including fetal) kidney, liver, heart, lung, pancreas, bone marrow, cornea, eye, bone, and skin or any subpart thereof and any other organ (or any subpart thereof, including that derived from a fetus) specified by the Secretary of Health and Human Services by regulation.[33]

NOTA established a national system for the matching of donor organs to potential recipients, the Organ Procurement and Transplantation Network (OPTN).[34] The OPTN includes all transplant centers, as well as all organ procurement organizations (OPOs),[35]

Transplantation Act" (1984), which was brought to a vote with an astonishing 90 co-sponsors from both major political parties.").

[30] Laurel R. Siegel, *Re-Engineering the Laws of Organ Transplantation*, 49 Emory L.J. 917, 946 (2000) ("Because they pertain to different areas of the law, the federal laws do not necessarily preempt the state laws. The federal laws, particularly NOTA, establish the nationwide organ procurement structure and dictate rules such as the prohibition of sales of organs. State laws, on the other hand, stemming from the UAGA, deal with consent and related procedures. Common law is also a factor, and it may collide with statutory law.").

[31] Patrick D. Carlson, *The 2004 Organ Donation Recovery and Improvement Act: How Congress Missed an Opportunity to Say "Yes" to Financial Incentives for Organ Donation*, 23 J. CONTEMP. HEALTH L. & POL'Y 136 (2006) ("Prior to the enactment of NOTA in 1984, organ donation and transplantation regulation traditionally had been exclusively a matter of state law. At the time of NOTA's passage, all fifty states and the District of Columbia had adopted, with minor variations, the Uniform Anatomical Gift Act (UAGA), drafted in 1968 by the National Conference of Commissioners on Uniform State Laws to encourage the making of anatomical gifts.").

[32] Daubert, supra note 16, at 463.

[33] 42 U.S.C.A. § 274e.

In 2014, HHS issued a final rule to add vascularized composite allografts (VCAs) to the statutory definition of "organ." VCAs include "intact vascularized body parts such as hands and faces." 78 FR 40033 (2014).

[34] 42 U.S.C.A. § 274.

[35] 42 U.S.C.A. § 273.

and is managed by the United Network for Organ Sharing (UNOS), a private, nonprofit entity which has served as the OPTN under contract with the U.S. Department of Health and Human Services (HHS) since 1986.[36] The OPTN is primarily responsible for developing equitable policies for organ allocation and administering the national transplant candidate waiting list.[37]

A central provision of NOTA, § 301(a), bans the buying and selling of human organs. NOTA imposes criminal penalties of up to $50,000 and five years in prison on any person[38] who "knowingly acquire[s], receive[s], or otherwise transfer[s] any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce."[39] Significantly, neither the Act nor its legislative history, which is discussed at greater length below, defines the term "valuable consideration." Both, however, "provide insight into the term's meaning by suggesting a congressional concern with the buying and selling of human organs for profit, rather than an attempt to prohibit all transactions in human organs that involve some element of exchange."[40]

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[36] UNITED NETWORK FOR ORGAN SHARING (UNOS), *National Organ Transplant Act Enacted 30 Years Ago,* http://www.unos.org/about/index.php?topic=newsroom&article_id=2889.

[37] Rick K. Jones, *The Gift of Life and "Diseases of Language": Recovering A Lost Distinction in Effectuating the Purpose of the National Organ Transplant Act's Prohibition on The Transfer of Human Organs for Valuable Consideration*, 80 Temple L. Rev. 1067, 1074–1075 (2007).

[38] NOTA's prohibition on the purchase or sale of body parts for transplantation applies to "any person." That includes both natural persons and legal persons (i.e., tissue banks and processors). Katz, *supra* note 11, at 952. Every "person" who receives body parts for use in transplantation is subject to NOTA's restrictions. *Id.* at 953.

[39] 42 U.S.C.A. §274e(a) (2000).

[40] Kieran Healy & Kimberly D. Krawiec, *Custom, Contract, and Kidney Exchange*, 62 DUKE L.J. 645, 661 (2012). NOTA is consistently interpreted as insufficiently broad to cover the sale of human gametes. Sarah Terman, *Marketing Motherhood: Rights and Responsibilities of Egg Donors in Assisted Reproductive Technology Agreements*, 3 NW J. L. & SOC. POL'Y 167, 12 (2008). In *Flynn v. Holder*, 684 F.3d 852 (9th. Cir. 2012), the Ninth Circuit held that NOTA does not prohibit the common practice of compensating blood donors. *Id.* at 862.

The Act explicitly states that valuable consideration "does not include the reasonable payments associated with the removal, transportation, implantation, processing, preservation, quality control, and storage of a human organ."[41] By including an exception for "reasonable payments," NOTA permits transplant surgeons, transporters, organ processors, and others to receive compensation for their services.[42] Given that § 301 is a criminal statute, it is appropriate to apply the rule of lenity in favor of a narrow reading and, therefore, to understand valuable consideration as the bald buying and selling of organs for money.[43]

2. NOTA's Legislative History

One major impetus for including the prohibition of organ purchases in NOTA was the ethical debate sparked by a high-profile proposal to broker human kidneys.[44] In September 1983, Dr. Barry Jacobs, a physician whose license to practice medicine had

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[41] 42 U.S.C.A. §274e(c)(2). The Act also includes an exception for "the expenses of travel, housing, and lost wages incurred by the donor of a human organ in connection with the donation of the organ." *Id.*

[42] Kristy L. Williams, Marisa Finley, & J. James Rohack, *Just Say No to NOTA: Why the Prohibition of Compensation for Human Transplant Organs in NOTA Should Be Repealed and A Regulated Market for Cadaver Organs Instituted*, 40 AM. J.L. & MED. 275, 291 (2014). This exception is essential, as it is hard (if not impossible) to imagine a distribution network that didn't cover expenses. However, as a result, even though the initial sale of an organ is prohibited, everyone involved in the process of organ transplantation, except for the donor, is able to profit. *Id*. Current jurisprudence recognizes a legal interest in the organ of each person in each transaction—with the exception of the donor. Boyer, *supra* note 7, at 334.

[43] Legality of Alternative Organ Donation Practices Under 42 U.S.C. § 274(e), 31 Op. Off. Legal Counsel (Mar. 28, 2007), available at http://www.justice.gov/sites/default/files/olc/opinions/2007/03/31/organtransplant.pdf, at 6.

[44] Williams, Finley, & Rohack, *supra* note 42, at 289. *See also* Carlson, *supra* note 31, at 158. Other motivations for NOTA included recent advances in transplant surgery, the FDA's approval of cyclosporine in 1983, the growing asymmetry between supply and demand of transplantable organs, and a series of public appeals by families seeking organs. Phil Gunby, *Bill Introduced to Thwart Kidney Brokerage*, 250 JAMA 2263, 2263 (1983).

previously been revoked following a conviction for Medicare mail fraud and the founder of International Kidney Exchange, Ltd., caught the attention of the national media.[45] Jacobs sent a brochure to 7,500 American hospitals offering to broker contracts between patients with end stage renal disease[46] and individuals—domestically and abroad—willing to sell a kidney.[47] He proposed to charge a sliding-scale brokerage fee and retain a profit for himself.[48] According to Jacobs, he contacted the FDA and other federal agencies to determine if laws or regulations prohibited his approach and to determine if a license was needed to import organs.[49] Some officials reportedly counseled against the brokerage proposal, but they did not find that it violated any existing regulations.[50] Although Jacobs never managed to get his business off the ground,[51] he came to represent "transplantation out of control, and anxieties about the misuse of medical power latched onto him, his business plan, and the entire notion of putting a monetary value on organs."[52]

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[45] Gross, *supra* note 17, at 178; *see also* Joralemon, *supra* note 29, 30. In a USA TODAY guest column, Jacobs colorfully wrote that "[c]ompensating the donor for blood or a kidney is the American way. . . . When it comes to deciding what to do with our bodies, Congress is not a better judge than the individual. . . . Only in the Soviet Union do human organs belong to the state." Gross, *supra* note 17, at 183.

[46] *See generally*, U.S. NATIONAL LIBRARY OF MEDICINE (NLM), NATIONAL INSTITUTES OF HEALTH (NIH), *End-Stage Kidney Disease*, http://www.nlm.nih.gov/medlineplus/ency/article/000500.htm.

[47] *Id.* The letter is reproduced in Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, Serial No. 98-70, 367 (1984).

[48] The person seeking a transplant would pay for the kidney and an additional $2,000 to $5,000 to Jacobs for his services. Note, Regulating the Sale of Human Organs, 71 VA. L. REV. 1015, 1015 (1985). Jacobs explained that if the "recipient could afford [it], without indigence—there would be a sliding scale brokerage fee that would cover the cost [International Kidney Exchange, Ltd.] would incur. Then what would be left from the brokerage fee would be used to advance the cost to those who couldn't afford it so they could purchase a kidney, go back to work, reimburse the fund, which would then have he money available for the next person." *Id.* at 241.

[49] Gunby, *supra* note 44, at 2263.

[50] *Id.*

[51] Joralemon, *supra* note 29, 30.

[52] Gross, *supra* note 17, at 185.

Against this backdrop,[53] then-Representative Albert Gore, Jr.,[54] Chair of the House Science and Technology Committee's Oversight Subcommittee, convened the first of a series of hearings that would culminate in enactment of NOTA in 1984.[55] In July and October of 1983, the House Committee on Energy and Commerce's Subcommittee on Health and the Environment held further hearings on transplant policy under the direction of Subcommittee Chairman Henry Waxman.[56] Although Gore was not a member of the Subcommittee, he played "a leading role in its hearings by providing extensive testimony about the challenges of organ allocation and transplant financing."[57]

Several major challenges emerged as focal points at these hearings. The introduction of the immunosuppressant cyclosporine meant that a lack of two resources—money and donor organs—was likely to limit the number of individuals who would benefit from organ transplantation.[58] An infrastructure to efficiently coordinate organ transfer

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[53] In addition to International Kidney Exchange, Ltd., an earlier organ brokerage program in the Northeast never got off the ground, and there may have been a similar effort in the Midwest. Gunby, *supra* note 44, at 2263.

[54] Gore's interest in transplant policy has been attributed to multiple factors. Gross, *supra* note 17, at 180 ("The Congressman had "learned that the most pressing problem in caring for end-stage renal disease was availability of suitable organs for transplant" during 1982 congressional hearings on dialysis and diet. The Congressman's exposure to the problem also became more personal "when one of his constituents sought Gore's help in securing an organ." Around the same time, a Yale pediatrics professor, Dr. Myron Genel, was "assigned" to Gore through the Robert Wood Johnson Health Policy Fellows Program. This new staff affiliate reportedly "press[ed] Gore to use his position as chair of an investigative subcommittee to highlight problems [regarding transplantation] and develop a federal government solution.""") (internal citations omitted).

[55] *Id.*

[56] *Id.* at 181 (noting that Waxman had an "unusually deep familiarity with transplantation" because he first attempted to improve the accessibility of transplantation as a member of the California State Senate).

[57] *Id.*

[58] *Id*. at 182.

was also missing.[59] These concerns had an ethical dimension: "[c]oncerns about differential access to transplant surgery and distributive justice . . . surfaced repeatedly as legislators probed the problems of procurement, financing, and organization."[60] Additionally, Congress felt that the buying and selling of organs ran counter to society's moral values.[61]

In his testimony, Gore described the buying and selling of organs as "just wrong,"[62] and explained that it "is against our system of values to buy and sell parts of human beings. It is against our system of values to auction off life to the highest bidder. . . . What we are talking about here is the gift of life and the real problem is how to persuade people to give life, not how to purchase it.[63] Gore's testimony reflected his concerns that a market for human organs would result in unethical commodification of the body, exploitation of the poor, and compromises to donor health and well-being.[64]

Gore's concerns were echoed by members of the Subcommittee as well as by others who testified before it. Representative Henry Waxman remarked that "the bill explicitly prohibits organ sales and imposes strict criminal penalties on those who would promote such practices. The specter of individuals coerced to sell their kidneys—placing their lives in jeopardy—represents a form of human exploitation foreign to our concepts of medical

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[59] *Id.*

[60] *Id.* at 182–183.

[61] Daubert, supra note 16, at 466.

[62] Hearings before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, House of Representatives, 98th Congress, 1st session, on H.R. bill 4080. Serial No. 98-70 (1984), at 128.

[63] *Id.*

[64] Carlson, *supra* note 31, at 158.

and social ethics."[65] Representative Thomas Bliley, Jr. spoke of "the ill-advised organ sales proposal."[66] Dr. Edward Brandt, Assistant Secretary for Health, presented the views of the administration.[67] He opposed the sale of human organs, believing "such activity is immoral and goes against the principles of medical ethics. [The Secretary] and I are particularly concerned about those persons willing to sell their organs who may not fully understand the serious consequences of their action."[68]

In the summary of the bill, the Senate Committee on Labor and Human Resources Report No. 98-382, states:

> It is the sense of the committee that individuals or organizations should not profit by the sale of human organs for transplantation. This is not meant to include blood and blood derivatives, which can be replenished and whose donation does not compromise the health of the donor. The current state of the law is uncertain with regard to the sale of organs, and the committee believes that legislation is necessary to clarify this issue. The committee believes that human body parts should not be viewed as commodities.[69]

The House Conference Report explains that the final bill "intends to make the buying and selling of human organs unlawful."[70]

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[65] Serial No. 98-70, *supra* note 62, at 89–90.

[66] *Id.* at 107.

[67] Barry Jacobs colorfully described Dr. Brandt as "sitting on his butt" at the start of his testimony. *Id*. at 238.

[68] *Id*. at 134. Samuel Gorovitz, a Professor of Philosophy, testified, "The risks to donors are greater than [Barry Jacobs] has admitted . . . . And the scheme makes a mockery of informed consent, as is evident to anyone familiar with Federal regulations protecting human subjects research, which reflect a sensitive awareness that desperate circumstances can be implicitly coercive, and that the provision of excessive inducements to the oppressed can constitute a violation of their autonomy." *Id*. at 279. He also stated, "At a time when we urgently need to nurture good relations with the nations of the third world, our international credibility would be dealt a severe blow by our tolerance of a plan according to which the poor in underdeveloped countries were exploited as a source of spare parts for rich Americans. Our antagonists behind the iron curtain would love such a public relations windfall – and they would be right." *Id.* at 282.

[69] *Id*. at 16–17.

[70] H.R. Conf. Rep. No. 98-1127, at 16.

At the signing, President Ronald Regan explained that "[t]his bipartisan legislation provides a framework that should help increase the overall supply of much needed organs and improve our ability to match donor organs with individuals in need off transplants. Over the last 3 years, I have urged the American people to remember that many lives could be saved through generous donations of life-saving organs. . . . This act will serve to support this ongoing work."[71]

As the legislative history makes clear, those involved in enactment of NOTA were motivated in part by moral concerns about commodification of the human body, as well as by the possibility for exploitation and coercion of donors. These ethical considerations underpinned the ban on exchanging human organs for valuable consideration. The Act defined "organ" to include tissue, overlooking key differences between organs and tissues—the topic to which we turn next—and failing to see the mismatch between the goals of the legislation and its practical effects when applied to tissues.

II. Key Differences Between Tissues and Organs

The basic unit of every living organism is the cell. It has recently been estimated that the human body has 3.72×10^{13} cells.[72] The number of cells—together with their type and size—ultimately defines the size, structure, and functions of an organism.[73] Some

[71] Ronald Regan, *Statement on Signing the National Organ Transplant Act*, October 19, 1984, http://www.presidency.ucsb.edu/ws/?pid=39282. The White House was particularly interested in pediatric liver transplantation, perhaps because First Lady Nancy Regan's father, Dr. Loyal Davis, was professional mentor to Thomas Starzl, a pioneering liver transplant surgeon. Gross, *supra* note 17, at 178.

[72] Eva Bianconi, Allison Piovesan, Federica Gacchin, et al., *An Estimation of the Number of Cells in the Human Body*, 40 ANNALS OF HUMAN BIOLOGY 463, 466 (2013) (reporting estimates in the literature from 10^{12} to 10^{16}).

[73] *Id*. at 463.

organisms are nothing more than free-living, single cells.[74] Slightly more complex life forms "are organized into masses or aggregates of similar cells with little evidence of cell specialization."[75] In higher organisms, like humans, cells are specialized to perform different functions.[76] A tissue is a collection of similar cells that are specialized to perform a particular function.[77] There are four basic types of tissue: connective tissue; epithelial tissue; nerve tissue; and muscle tissue, of which there are three types: smooth, striated, and cardiac.[78] Groups of different tissues can be organized further into complex organs that perform specialized functions.[79]

Although bones and skin—to pick but two examples—are classified as "organs" according to medical definitions, they are considered "tissues" for purposes of organ and tissue donation.[80] According to organdonor.gov, which is run by HHS, organs that can be donated include the lungs, heart, liver, pancreas, kidneys, and intestines.[81] Tissues that can be donated include the cornea, whole eye, skin, heart valves, veins, bone, cartilage, and connective tissues.[82] Going forward I will use the terms "organ" and "tissue" in the manner consistent with donation practices.

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[74] *Id.* (e.g., yeasts and bacteria).

[75] NUFFIELD COUNCIL ON BIOETHICS, HUMAN TISSUE: ETHICAL AND LEGAL ISSUES, 17 (1995) (e.g., sponges).

[76] *Id.*

[77] *Id.*

[78] NATIONAL LIBRARY OF MEDICINE (NLM), *Tissue Types*, http://www.nlm.nih.gov/medlineplus/ency/imagepages/8682.htm.

[79] NUFFIELD COUNCIL, *supra* note 75, at 18.

[80] *See, e.g.*, HHS, *What Can Be Donated?*, http://www.organdonor.gov/about/donated.html.

[81] *Id.*

[82] *Id.*

NOTA's definition of "human organ," quoted above, encompasses both organs and tissues. Although tissue transplantation is superficially similar to organ transplantation, they are meaningfully different.[83] Here, I will highlight differences along five dimensions, focusing primarily on the differences between cadaveric organ donation and cadaveric tissue donation. These dimensions are: the size of the respective donor pools; procurement, storage and processing; allocation; uses; and regulation. While some of these differences are the result of inherent characteristics of organs and tissues, others are the result of the legal frameworks that have been put in place around organs and tissues respectively.

A. Difference 1: Size of Donor Pools

Tissues and organs can be procured from living donors.[84] Most donations, however, take place after the donor has died.[85] A far greater number of people are potential cadaveric tissue donors than potential cadaveric organ donors.[86] Whereas only 5% of all deaths are eligible for organ donation, 95% of all deaths are eligible for tissue donation.[87]

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[83] *Cf*. Michelle Oberman, *When the Truth is Not Enough: Tissue Donation, Altruism, and The Market*, 55 DEPAUL L. REV. 903, 905 (2006).

[84] For example, a living donor may be able to donate a segment of liver, a lobe of lung, a section of intestine, a portion of pancreas, or a single kidney without being deprived of an essential organ. GIFT OF LIFE DONOR PROGRAM, *What is Living Donation, http://www.donors1.org/livingdonation/livingdonationfaq/.*

[85] *Id.*

[86] Oberman, *supra* note 83, at 907. Oberman notes that "[f]ederal law governing organ transplantation helped to expand the supply of available tissue by requiring hospitals to notify the regional Organ Procurement Organization (OPO) in the event of a potential donor's death. By making requests for donation routine, these regulations had the indirect effect of enhancing the availability of tissue as well." *Id.* (internal citations omitted).

[87] UW ORGAN AND TISSUE DONATION, *Organ and Tissue Donation Differences*, http://www.uwhealth.org/organ-donation/organ-and-tissue-donation-differences/13825.

Limitations—legal, ethical, and biological—on who can donate organs restrict the supply of potential organ donors but have much less effect on the pool of potential tissue donors.

The "dead donor rule" is an "ethical and legal constraint that holds that doctors cannot remove vital organs necessary to keep bodies alive from patients until they are dead."[88] Under the Uniform Determination of Death Act (UDDA),[89] which has been adopted by forty-four states and the District of Columbia,[90] "[a]n individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead."[91] This determination must be made in accord with accepted medical standards.[92] Brain dead individuals, those in category (2), make ideal organ donors, as their organs continue to receive oxygenated blood from their still-beating heart.[93] By contrast, the organs of patients who experience cardiac death, those in category (1), begin to suffer from

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[88] Seema K. Shah, *Piercing the Veil: The Limits of Brain Death as a Legal Fiction*, 48 U. MICH. J.L. REFORM 301, 308 (2015).

[89] Unif. Determination of Death Act § 1.

[90] Shah, *supra* note 88, at 308.

[91] Unif.Determination of Death Act § 1.

[92] *Id.*

[93] Gary Greenberg has pointed out the resulting paradox: "the need for both a living body and a dead donor." Gary Greenberg, *As Good As Dead: Is There Really Such a Thing as Brain Death?*, THE NEW YORKER August 13, 2001. http://www.newyorker.com/magazine/2001/08/13/as-good-as-dead. It has been estimated that the pool of brain dead potential organ donors in the United States falls between 10,500 and 13,800. Ellen Sheehy, Suzanne L. Conrad, Lori E. Brigham, et al, *Estimating the Number of Potential Organ Donors in the United States*, 349 NEJM 667, 670 (2003).

ischemia.[94] As a result, the yield of transplantable organs from donation after cardiac death is generally not as favorable as that with donation after brain death.[95]

While the pool of potential organ donors is highly restricted, most deceased persons can be tissue donors.[96] The total number of organ donors—living and dead—was 14,412 in 2014.[97] By contrast, approximately 30,000 donors provide tissue each year.[98] Whereas one person can save up to eight lives through organ donation, one person can enhance the lives of fifty or more people through tissue donation.[99] This is because many more tissues than organs can be recovered from each donor. Depending on what tissues are recovered,

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[94] *See generally* J.L. Bernat et al., *Report of a National Conference on Donation After Cardiac Death*, 6(2) AM. J. OF TRANSPLANTATION 281 (2006) (discussing warm ischemic time).

[95] D.J. Reich et al, *ASTS Recommended Practice Guidelines for Controlled Donation after Cardiac Death Organ Procurement and Transplantation*, 9 AM. J. TRANSPLANTATION 2004, ___ (2009). Reich et al. also suggest that outcomes might not be as favorable for recipients of DCD organs. *Id.* The subsequent literature is mixed. *See, e.g.,* C.L. Jay et al*, Comparative Effectiveness of Donation After Cardiac Death Versus Donation After Brain Death Liver Transplantation: Recognizing Who Can Benefit*, 18 LIVER TRANSPL. 630 (2012) ("For patients with a MELD score <15, DCD transplantation resulted in greater costs and reduced effectiveness.").

[96] HHS, *Organ Donation*, http://www.organdonor.gov/about/organdonation.html. *See, e.g.*, Eye Bank Association of American, *Frequently Asked Questions*, http://www.restoresight.org/about-us/frequently-asked-questions/ ("Who can be a donor? Anyone can. The great thing about corneal tissue is that everyone is a universal donor. Your blood type does not have to match. It doesn't matter how old you are, what color your eyes are or how good your eyesight is. Aside from those suffering from infections or a few highly communicable diseases such as HIV or hepatitis, most people are suitable donors.").

[97] HHS, *Organ Procurement and Transplantation Network*, http://optn.transplant.hrsa.gov. There were nearly 6,000 transplants from living donors, and there were more than 8,500 deceased donors. Donate Life America, *Statistics*, http://donatelife.net/statistics/ (last visited Feb. 24, 2016).

[98] HHS, *Organ Donation*, http://www.organdonor.gov/about/organdonation.html. A 1995 study reported that of 603 donor-eligible families that were asked to donate organs, tissues, or corneas, slightly more than 34% agreed to donate something. Of the 170 organ-eligible cases, only 46.5% donated. Fewer tissue and kidney requests were granted (34.5 and 23.5%, respectively). Laura A. Simioff, et al., *Public Policy Governing Organ and Tissue Procurement in the United States: Results from the National Organ and Tissue Procurement Study*, 123 ANN. INTERN. MED. 10, 14 (1995).

[99] HHS, *Organ Donation*, http://www.organdonor.gov/about/organdonation.html.

a cadaver can yield up to twenty bones and tendons, as well as 4 square feet of skin, and several heart valves.[100]

B. Difference 2: Procurement, Processing, and Storage

Whereas time is of the essence in organ donation,[101] it is much less pressing in tissue donation. This is evident in the respective practices related to procurement, storage, and processing of organs and tissues.

Federal regulations require hospitals to notify their local OPO of every patient whose death is imminent or who has died.[102] The hospital will give the OPO information about the dying or deceased individual to confirm his or her suitability to be a donor. The OPO is tasked with determining "medical suitability for organ donation and, in the absence of alternative arrangements by the hospital, the OPO determines medical suitability for tissue and eye donation." [103]

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[100] Mark Katches, William Heisel, & Ronald Campbell, *The Body Brokers: Part 1 - Assembly Line*, THE ORANGE COUNTY REGISTER, April 17, 2000.

[101] HHS, *Organ Donation: The Process*, http://organdonor.gov/about/organdonationprocess.html#process4 ("Organs must get to their new homes very quickly as they can remain healthy only for short periods of time after removal from the donor.").

[102] 42 CFR 3, Subpart C, § 482.45, Condition of Participation: Organ, tissue and eye procurement.

[103] *Id*. The OPO or tissue bank will review the donor's medical records, inquire into the donor's social history, and test the donor for transmissible diseases. Katz, *supra* note 11, at 960–961. Outside the hospital, tissue banks might learn about potential donors from coroners, medical examiners, or funeral home directors. *Id.* at 959. If an individual dies at home, their organs cannot be transplanted; they may, however, be tissue donors. DONATE LIFE NORTH CAROLINA, *Frequently Asked Questions*, https://www.donatelifenc.org/content/frequently-asked-questions#can-my-organs-be-used.

If the patient is a potential candidate for organ donation, an OPO representative immediately travels to the hospital[104] and secures legal consent.[105] If the decision is made to donate after cardiac death, organ recovery may occur if death occurs within the established timeframe after withdrawal of life-sustaining measures.[106] If a donor has been declared brain dead, the organ donor is maintained on life support in order to ensure the viability of his organs for transplantation.[107] The OPO representative arranges for recovery of the organs, which is performed in the sterile environment of the operating room.[108] Prior to removal from the donor, "each organ is flushed free of blood with a specially prepared ice-cold preservation solution that contains electrolytes and nutrients. The organs are then placed in sterile containers, packaged in wet ice, and transported to the recipient's transplant center."[109] Preservation in this manner buys time, which is essential for organizing staff and facilities, transporting organs, and performing the many procedures necessary for transplantation.[110] In general, "storage times are 30 hours or less for a kidney, less than 12 hours for a pancreas or liver, and less than 6 hours for a heart or

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[104] HHS, *Organ Donation: The Process*, http://organdonor.gov/about/organdonationprocess.html#process4.

[105] If the deceased had enrolled as a donor, that will serve as legal consent. If not, the OPO will seek consent from the next of kin. *Id*.

[106] S*ee generally,* Robert Steinbrook, *Organ Donation After Cardiac Death*, 357 NEJM 209 (2007).

[107] *See generally* D.W. McKeown, R.S. Bonser, & J.A. Kellum*, Management of the Heartbeating Brain-Dead Organ Donor*, 108 BR. J. ANAESTH. i96 (2012); *see also* UNOS, *Critical Pathway for the Organ Donor*, https://www.unos.org/docs/Critical_Pathway.pdf (recommending physiological goals and an active approach to donor management).

[108] HHS, *Organ Donation: The Process*, http://organdonor.gov/about/organdonationprocess.html#process4.
[109] New York Presbyterian, *Transplantation: Organ Transplant Process*, http://nyp.org/services/transplantation-surgery/organ-transplant-process.html.

[110] Edgardo E. Guibert, Alexander Y. Petrenko, Cecilia L. Balaban, Alexander Y. Somov, Joaquin V. Rodriquez, & Barry J. Fuller, *Organ Preservation: Current Concepts and New Strategies for the Next Decade*, 38(2) TRANSFUS. MED. HEMOTHER. 125, 126 (2011).

lungs."[111] Storage times vary in light of the relative speed with which organs begin to deteriorate.[112]

If the deceased individual is a suitable tissue donor, and consent is secured, the OPO or tissue bank arranges for the tissue to be recovered within twenty-four hours of the donor's death.[113] Tissues may be removed in the operating room after organs are recovered,[114] elsewhere in the hospital, or in other locations, such as a funeral home or morgue[115] under aseptic techniques.[116] Tissues typically "go through several levels of handling before transplantation."[117] Processors, typically for-profit organizations,[118] take the raw tissues from the OPO or tissue bank and transform them into allografts for implantation.[119] The methods used by processors may be patented and/or the allografts

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[111] UNIVERSITY OF MICHIGAN TRANSPLANT CENTER, *FAQ: 24. How Long Can Donated Organ Last Outside the Body?*, http://www.transweb.org/faq/q24.shtml.

[112] *Id.* Because organs must be transplanted as quickly as possible, they are given first to people who live near the hospital where organs are recovered from the donor. The "[d]istance between the donor's hospital and the potential recipients's hospital is more important for matching hearts and lungs than it is for kidneys or livers." HHS, *Organ Matching Process*, http://www.organdonor.gov/about/organmatching.html.

[113] Oberman, *supra* note 83, at 910. Many OPOs operate as tissue banks and, thus, are equipped to retrieve and store human tissue. Other OPOs work with independent tissue banks, which will be notified of the family's consent and will then undertake the retrieval process. *Id*.

[114] HHS, *Organ Donation: The Process*, http://organdonor.gov/about/organdonationprocess.html#process4.

[115] Joseph Shapiro and Sandra Bartlett, *The Seamy Side of the Human Tissue Business*, National Public Radio, http://www.npr.org/2012/07/19/156988089/the-seamy-side-of-the-human-tissue-business (2012).

[116] Allograft Possibilities, *About Tissue* Transplant, http://allograftpossibilities.org/about-tissue-transplant/. Bone is replaced with PVC pipe to preserve the body's appearance for open-casket funerals. *See, e.g.,* ANNIE CHENEY, BODY BROKERS: INSIDE AMERICA'S UNDERGROUND TRADE IN HUMAN REMAINS (2007).

[117] Siminoff, Traino, & Gordon, *supra* note 1, at 961.

[118] Buck, *supra* note 12, at 125. Buck notes that for-profit processors have a strong hold on the industry due to their patented processing techniques. *Id.* Some of the most important advances in the tissue industry are attributable to for-profit tissue banks. *Id.* at 125–126.

[119] For example, AlloSource "offer[s] more than 200 types of precise bone, skin, soft-tissue and custom-machined allografts for use in an array of life-saving and life-enhancing medical procedures." ALLOSOURCE, *About AlloSource*, http://www.allosource.org/about-allosource/; *see also* ALLOSOURCE, *Products*, http://www.allosource.org/products/.

themselves may be patented.[120] Once processed, tissues can be stored for an extended period of time before being used.[121] Donated heart valves can be stored for up to 10 years, and other donated tissues can be stored for up to five years.[122]

In exchange, for its work, the OPO or tissue bank will receive a "reasonable payment,"[123] known as a Standard Acquisition Charge, to cover expenses.[124] Fees for organ retrieval vary across the country; for example, fees for a kidney may vary from $16,000 to $30,000.[125] A typical tissue donor produces $14,000 to $34,000 in fees for a non-profit OPO.[126] After a tissue processor has treated and rendered the tissue transplantable, the

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[120] Buck, *supra* note 12, at 125.

[121] Williams, Finley, & Rohack, *supra* note 44, at 291.

[122] NATIONAL HEALTH SERVICE BLOOD AND TRANSPLANT, *Tissue Donation*, http://www.nhsbt.nhs.uk/tissuedonation/how-to-become-a-donor/tissue-donation-after-death/; *see also* THE BLOOD AND TISSUE CENTER OF CENTRAL TEXAS, *Tissue Donation FAQs*, http://www.inyourhands.org/tissue-center/learn-more/tissue-donation-faq/ ("If tissues are packaged and stored properly, most can be kept from 5 to 10 years, depending on the procedures set forth by the processing agency.").

[123] *See* Katches, Heisel, & Campbell, *supra* note 100. ("Companies and tissue banks step around the law by charging marked-up fees to handle and process the body parts. . . . Judy Perkins, executive director of the University of California, San Diego, Regional Tissue Bank, calls fees a euphemism for sales.").

[124] Katz, *supra* note 11, at 961–962. Katz explains that the fee "permits the tissue bank to recoup its actual outlays on tissue recovery, aftercare, education, and 'other costs associated with operating a tissue recovery program.' Typically, these fees also include a small percentage or margin that provides the tissue bank with excess revenue for future expansions, savings, and other needs." *Id.* at 962.

[125] Advisory Committee on Organ Transplantation, Spring Meeting Notes (May 4-5, 2006), http://organdonor.gov/legislation/acotmay2006notes.html (last visited Feb. 22, 2016).

[126] Oberman, *supra* note 83, at 909.

Buck, *supra* note 12, at 149 ("[M]oney changes hand from the point of tissue procurement to the final transplantation of the tissue. First, a hospital will charge the procurement agency for the use of the operating room and supplies, a charge which is typically between $500 and $3000. The tissue recovery team receives between $250 and $400 for its services, and if transportation was needed to get to the hospital, $1000 to $3000 may be charged. The tissue recovery team then sends the tissue to the tissue bank for processing. The recovery team will bill each tissue bank a Standard Acquisition Charge ("SAC"), which covers "the costs of tissue recovery, administrative costs, . . . and other costs associated with operating a tissue recovery program." "SACs vary throughout the United States," and differ depending upon the type of tissue collected. Typically, musculoskeletal tissues command fees of $5500, veins, $600 per vein, and $250-$500 per square foot of skin. Knee tendons, which take minutes to remove from a cadaver, can command a revenue of $2,500

tissue will gain tremendous value.[127] For instance, one cadaver can be worth nearly $220,000.[128] These gains are realized when the tissues are distributed to doctors, hospitals, or others who use the end products.[129]

C. Difference 3: Allocation Considerations

The allocation of organs takes into account medical, logistical, and ethical considerations. As the market for tissues currently exists, these concerns are not nearly as relevant to tissue allocation.

Many of the criteria for matching organs from deceased donors to potential recipients are the same for all organs.[130] Though there is some variation, the criteria usually include: "blood type, body size, severity of patient's medical condition, distance between the donor's hospital and the patient's hospital, the patient's waiting time, and the availability of the potential recipient (e.g., the patient can be contacted and has no current infection or other temporary reason that transplant cannot take place)."[131] Matching is intended primarily to avoid transplant rejection, a process by which the recipient's immune

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each, while valves cut out of donated hearts and later sold as transplants go for more than $7,000 each. Once the human tissue is at the processor, all expenses incurred are part of the fees which "the processor charges to the hospital or other purchaser."") (internal citations omitted).

[127] Siminoff, Traino, & Gordon, *supra* note 1, at 961.

[128] *Id.* ("[S]kin, tendons, heart valves, veins and corneas are listed at about $110,000. Add bone from the same body, and one cadaver can be worth about $220,000."); *see also*, Jean-Paul Pirnay, Alain Vanderkelen, Martin Zizi, Daniel De Vos, Thomas Rose, Geert Laire, Nadine Ectors, & Gilbert Verbeken, *Human Cells and Tissues: The Need for a Global Ethical Framework*, http://www.who.int/bulletin/volumes/88/11/BLT-09-074542-table-T1.html (table comparing prices of human cell and tissue products between Belgium and the U.S.).

[129] Siminoff, Traino, & Gordon, *supra* note 1, at 961.

[130] HHS, *Organ Matching Process*, http://www.organdonor.gov/about/organmatching.html.

[131] *Id.*

system attacks the transplanted organ.[132] NOTA, as well as subsequent federal regulation, calls on the OPTN to emphasize fair and equitable access to organ transplantation.[133]

Although transplant surgeons and hospitals doubtlessly profit from organ transplantation,[134] tissue transplantation is a multibillion-dollar industry.[135] A "problematic consequence of the lucrative nature of the market in human tissue has been the emergence of a variety of alliances and exclusive partnerships between for-profit tissue processors and non-profit tissue banks in order to stabilize or increase their supply."[136]

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[132] NLM, *Transplant Rejection*, http://www.nlm.nih.gov/medlineplus/ency/article/000815.htm (last visited Mar.2, 2016).

[133] *E.g.*, 42 U.S.C.A. § 274(b)(2)(D) ("assist organ procurement organizations in the nationwide distribution of organs equitably among transplant patients"). This is not to say that transplants are inexpensive. In 2011, "[t]he average billed charges per transplant . . . were $262,900 for a kidney transplant, $289,400 for a pancreas transplant, $561,260 for a single lung transplant, $277,100 for a liver transplant, $997,700 for a heart transplant, and $1,206,800 for the transplant of an intestine." Williams, Finley, & Rohack, *supra* note 44, at 308.

[134] In *Flynn*, the Ninth Circuit quoted Professor Leon Kass as saying, "Although we allow no commerce in organs, transplant surgeons and hospitals are making handsome profits from the organ-trading business." *Flynn*, *supra* note 40, at 861.

[135] *E.g.,* Boyer, *supra* note 7, at 331.

Executives of tissue banks routinely earn six-figure salaries. Musculoskeletal Transplant Foundation, one of the largest nonprofit tissue banks in the country, disclosed in its Form 990 for 2000 that it paid its CEO a salary of $367,951. CALIFORNIA SENATE OFFICE OF RESEARCH, TISSUE DONATIONS: ISSUES AND OPTIONS IN OVERSIGHT, REGULATION AND CONSENT, 21 (2003). Pacific Coast Tissue Bank, a nonprofit located in Los Angeles, paid its president $427,160 that same year, down from $533,450 in 1997 and 1998. *Id.* at 22.

[136] Oberman, *supra* note 83, at 912. In some instances, for-profit tissue processors are establishing non-profit tissue banks. *See, e.g.*, Buck, *supra* note 12, at 126 ("Today it is the norm for non-profit tissue banks and for-profit banks to create supply agreements, processing contracts, and formal partnerships."); Katz, *supra* note 11, at 967 ("At least two for-profit processors, Osteotech and RTA, have started nonprofit tissue banks in order to secure a steady and robust supply of tissue for processing."); Mark Katches, Liz Kowalczyk, & Ronald Campbell, *Pioneers* THE ORANGE COUNTY REGISTER, April 17, 2000 (describing how El Gendler co-founded Pacific Coast Tissue Bank, a non-profit that seeks donations, and also co-founded a private for-profit bone-processing firm that gets its materials from Pacific Coast).

Another problematic consequence of the lucrative market in human tissue has been intentional misconduct in the highly lucrative tissue procurement industry. Michael Mastromarino was a dental surgeon who, after becoming addicted to drugs and losing his license, got into the human tissue business. *E.g.,* Patterson, *supra* note 145. One of the more vivid details of Mastromarino's crime was stealing body parts from the cancer-riddled body of Alistair Cooke, famed host of *Masterpiece Theatre*. *Id.* Mastromarino pled guilty to body stealing and was convicted of faking documents. *Id*. Philip J. Guyett Jr. pled guilty to falsifying records so he could sell tissue from corpses that were "according to court documents, riddled with cancer, or showed signs

One result of these partnerships is that hospitals have difficulty securing enough skin to help burn victims, as donated skin is allocated to more profitable plastic-surgery products.[137] Thus, potential profits rather than (roughly) prioritarian considerations[138] shape how donated tissues are ultimately allocated. Tissue recipients do not have to be matched to their donors, and rejection is not generally a concern.[139]

D. Difference 4: Uses

Vital organ transplants are life saving. In 2014, 29,533 individuals received organ transplants.[140] Yet, on average, 21 people die each day waiting for transplants due to the asymmetry between supply and demand.[141] A particularly vivid metaphor is that the

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of intravenous drug use. Philip J. Guyett Jr., HEADS SHOULDERS, KNEES, & BONE$, (2011) (detailing "a "body broker's" thirteen year journey through the legal and lucrative body parts business); *see also* Annie Cheney, BODY BROKERS: INSIDE AMERICA'S UNDERGROUND TRADE IN HUMAN REMAINS (2006).

[137] William Heisel, Mark Katches, & Liz Kowalczyk, *The Body Brokers: Part II - Skin Merchants*, THE ORANGE COUNTY REGISTER, April 17, 2000. The skin burn victims need goes to two companies that have contracts with many of the largest tissue banks. *Id*. The companies buy all of the skin the tissue banks harvest and transform it into plastic-surgery products. *Id.*

[138] For a general discussion and critique of how organs are allocated, *see* Govind Persad, Alan Wertheimer, & Ezekiel J. Emanuel, *Principles for Allocation of Scarce Medical Interventions*, 373 LANCET 423, (2009).

[139] MUSCULOSKELETAL TRANSPLANT FOUNDATION (MTF), *Donation FAQs*, http://www.mtf.org/donor_faq.html; THE BLOOD AND TISSUE CENTER OF CENTRAL TEXAS, *Tissue Donation FAQs*, http://www.inyourhands.org/tissue-center/learn-more/tissue-donation-faq/ ("Can donated tissue be rejected by the recipient's body? In contrast to organ donation, tissue grafts do not have to be matched to recipients' blood type. Rejection of tissue grafts is uncommon.").

[140] HHS, *Organ Procurement and Transplantation Network*, http://optn.transplant.hrsa.gov. As of March 2015, 123,296 people need an organ transplant; 78,013 people are active waiting list candidates. *Id.*

[141] HHS, *The Need Is Real: Data*, http://www.organdonor.gov/about/data.html. It has been suggested that this number is too low because it does not take into account the 4,000 plus individuals who are removed from the waiting list each year because they are "too sick to transplant." DONATE LIFE AMERICA, *Deaths Equivalent to 22 Jumbo Jets Crashing Every Year Due to Organ Donor Shortage—Press* Release, http://donatelife.net/deaths-equivalent-to-22-jumbo-jets-crashing-every-year-due-to-organ-donor-shortage-press-release/.

number of people who die each year before they can receive an organ transplant is "equivalent [to] 22 jumbo jets crashing every year with no survivors."[142]

By comparison, millions of patients receive tissues each year.[143] These tissues may be instrumental in healing. Unlike organ donations, however, tissue donations are rarely life saving.[144] More often, they are life enhancing for the recipient.

> For spinal fusions and the repair of fractures, bone is in greatest demand, but veins may be used for bypass in heart surgery. The membrane around the heart can reupholster the brain after neurosurgery, and the membrane around the muscles of the thigh can sling up sagging bladders to control incontinence. Tendons and ligaments can return mobility. Corneas can restore clear vision. Cartilage can help in facial remodeling. Dead skin can replace burned skin. And collagen can fill wrinkles, plump lips, revive youthful appearance.[145]

As mentioned at the outset, donated tissue might also be used in "elective plastic surgery, like a penis enlargement procedure."[146]

E. Difference 5: Regulation

The tissue industry is relatively unregulated as compared to the organ industry.[147]

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[142] DONATE LIFE AMERICA, *supra* note 141.

[143] John S. DePaola and James M. Barbeau, *Enhanced Tracking of Tissue for Transplantation*, 309 JAMA 443, 443 (2013).

[144] Mark Katches, William Heisel, & Ronald Campbell, *The Body Brokers: Part 1 - Assembly Line*, THE ORANGE COUNTY REGISTER, April 17, 2000 ("Families are led to believe they are giving the gift of life. . . . The products are rarely life-saving as advertised.").

[145] Randall Patterson, *The Organ Grinder*, NEW YORK MAGAZINE (2006). Cadaveric skin is used repair damaged vocal cords; bone is used in orthopedic and dental surgery; tendons, cartilage, and ligaments are used to treat sports injuries; cadaveric heart valves replace damaged valves; donated skin and adipose tissue may be used for cosmetic purposes—including enlarging penises, smoothing wrinkles, and plumping lips. Laura A. Siminoff & Heather M. Traino, *Consenting to Donation: An Examination of Current Practices in Informed Consent for Tissue Donation in the United States*, 14 CELL TISSUE BANK 85, 85 (2013).

[146] Shapiro, *supra* note 1.

There are fifty-eight federally designated OPOs throughout the United States and its territories.[148] OPOs are non-profit organizations[149] that must be certified by the Centers for Medicare and Medicaid Services (CMS) and abide by CMS regulations.[150] They are the only organizations that can recover organs from deceased donors for transplantation.[151] The Health Resources Services Administration (HRSA), an agency of HHS, "oversees the transplantation of vascularized human organs through the OPTN, which sets policies related to procurement, transplantation, allocation, and outcomes reporting of human organs."[152] In addition, CMS has developed Conditions of Participation for hospitals that wish to be eligible for Medicare reimbursement for transplant services.[153] These Conditions of Participation are particularly influential because "[m]ost commercial payors

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[147] Katz, *supra* note 11, at 951; *see also*, Joseph Shapiro and Sandra Bartlett, *Little Regulation Poses Problems Tracking Tissue*, National Public Radio, http://www.npr.org/2012/07/18/156933032/little-regulation-poses-problems-tracking-tissue (2012) ("An investigation by reporters from NPR and the International Consortium of Investigative Journalists — a network of reporters around the world — found that there's little scrutiny at key points in the tissue donation and transplant process. But David Smith, president of the American Association of Tissue Banks, the industry trade group, disagrees with that finding. "We are very highly regulated," he says, noting that medical advances with tissue come so quickly that regulators have a hard time keeping up or staying out of the way. "That's what we worry about. Will the regulations affect our ability to come up with new ideas?"").

[148] ASSOCIATION OF ORGAN PROCUREMENT ORGANIZATIONS, *About* OPOs, http://www.aopo.org/about-aopos/.

[149] HHS, *Organ Procurement and Transplantation Network*, http://opotxfind.hrsa.gov/Search_OPO_OTC.aspx.

[150] HHS, *Organ Procurement Organizations*, http://organdonor.gov/materialsresources/materialsopolist.html.

[151] *Id.*

[152] 78 FR 40033 (2014).

[153] HHS, *Medicare Program; Hospital Conditions of Participation: Requirements for Approval and Re-Approval of Transplant Centers to Perform Organ Transplants*, Federal Register, Vol. 72, No. 61, 15198 (2007).

follow CMS' lead regarding transplant center regulation."[154] Programs that do not obtain Medicare certification must receive approval from the OPTN in order to receive organs.[155]

Federal law does not require tissue banks and processors to be non-profit or tax-exempt, nor does it grant tissue banks a monopoly over tissue recovery within a designated geographic area.[156] The American Association of Tissue Banks (AATB) is the accrediting body for tissue banks, and these are voluntary accreditations.[157] Although the AATB has said that the "vast majority" of banks recovering traditional tissues are accredited by the AATB, investigations suggest that only one-third are actually accredited by the AATB.[158] The FDA's Center for Biologics Evaluation and Records (CBER) regulates human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient under 21 C.F.R. Parts 1270 and 1271.[159] Tissue establishments are required to

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[154] M.M. Abecassis, R. Burke, A.B. Cosimi, et al, *Transplant Center Regulations—A Mixed Blessing? An ASTA Council Viewpoint*, 8 AM. JOURNAL OF TRANSPLANTATION 2496, 2496 (2008).

[155] *Id.* at 2497.

[156] Katz, *supra* note 11, at 956. Though the law does not require it, only non-profit agencies are engaged in soliciting donations and retrieving tissue from human cadavers. *Id.* at 908. There are, however, close relationships between non-profits and for profit tissue processors. *See supra* note 136.

[157] American Association of Tissue Banks, *Accreditation (Institutional Membership)*, http://www.aatb.org/Accreditation.

[158] *See* Kate Wilson, Vlad Lavrov, Martina Keller, Thomas Maier, & Gerard Ryle, *Human Corpses are Prize in Global Drive for Profits*, THE INTERNATIONAL CONSORTIUM OF INVESTIGATIONAL JOURNALISTS, http://www.icij.org/human-corpses-are-prize-global-drive-profits (2012).

[159] FDA, *Tissue & Tissue Products*, http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/ ("Parts 1270 and 1271 require tissue establishments to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records. FDA has published three final rules to broaden the scope of products subject to regulation and to include more comprehensive requirements to prevent the introduction, transmission and spread of communicable diseases.").

For background on how the FDA slowly came to regulate tissue banking, *see* R. Alto Charo, *Skin and Bones: Post-Mortem Markets in Human Tissue*, 26 NOVA L. REV. 421, 442–449 (2002) (discussing the evolution of the FDA's regulation of tissue-banking); Williams, *supra* note 11, at 409–421 (tracing the FDA's reactions to the development of a human tissue industry).

register and list their tissue-based products with FDA.[160] The typical tissue bank operates for nearly two years before the FDA first inspects it.[161] Firms that make medical products out of human tissues are required to report only the most serious adverse events they discover.[162] Only a handful of states require that tissue banks be licensed, and "even fewer states" inspect tissue banks.[163]

III. Understanding the Ethical Challenges Posed By Tissues

NOTA's various provisions—and in particular the ban on exchanging human organs for valuable consideration—were underpinned by ethical concerns related to commodification, exploitation, and coercion. Due to the differences between tissues and organs outlined above, several of the ethical aims of the Act are not presently realized by regulating organs and tissues in the same way. Moreover, not all of the ethical aims of NOTA are necessarily appropriate for cadaveric tissues.

A. Commodification

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[160] 21 CFR Part 1271 (2001) (requiring human cells, tissue, and cellular and tissue-based product establishments to register with the FDA).
[161] Wilson, Lavrov, Keller, Maier, & Ryle, *supra* note 158.

[162] *Id.*

[163] Katz, *supra* note 11, at 956.

The term "commodification" describes the actual buying and selling of something.[164] The rhetoric of non-commodification asserts that the buying and selling of organs would erode our respect for human life, and allowing bargained for exchanges would displace civic mindedness.[165]

> The altruistic experience of the donor in being responsible (perhaps) for saving a stranger's life is said to bring us closer together, cementing our community in a way that buying and selling cannot. . . . From the recipient's perspective, it is said that knowing one is dependent on others' altruism rather than on one's own wealth creates solidarity and interdependence, and that this knowledge of dependence better preserves and expresses the ideal of sanctity of life.[166]

NOTA was intended as a bulwark against commodification,[167] and was drafted to reflect the belief that "individuals or organizations should not profit by the sale of human organs for transplantation"[168]

Under NOTA, a donor may give away but not sell his or her tissues. From the donor's perspective, tissues are market inalienable.[169] Nevertheless, as discussed above,

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[164] Margaret J. Radin, *Market-Inalienability*, 100 HARVARD L. REV. 1849, 1859 (1987). Professor Radin also offers a broader construction: "Broadly construed, commodification includes not only actual buying and selling, but also market rhetoric, the practice of thinking about interactions as if they were sale transactions, and market methodology, the use of cost-benefit analysis to judge these interactions." *Id.*

[165] *See, e.g.*, *id*. at 1914 ("The altruistic experience of the donor in being responsible (perhaps) for saving a stranger's life is said to bring us closer together, cementing our community in a way that buying and selling cannot. . . . From the recipient's perspective, it is said that knowing one is dependent on others' altruism rather than on one's own wealth creates solidarity and interdependence, and that this knowledge of dependence better preserves and expresses the ideal of sanctity of life.").

[166] *Id*. at 1914 (characterizing the work of Richard Titmuss).

[167] *E.g.*, David Horton, *Indescendibility*, 102 CAL. L. REV. 543, 553 (2014).

[168] S. REP. 98-382, at 16-17 (1984).

[169] Radin, *supra* note 164, at 1852–1853.

there are many intermediaries between tissue donors and recipients.[170] Fees change hands at each stage of the tissue transplant process subsequent to donation.[171] As a result, "some tissue[s] come to resemble a commercial product."[172] While many transactions are protected under the "reasonable payment" exception,[173] some intermediaries exploit the "reasonable payment" loophole by recouping more than their expenses plus normal profits—that is, they receive unreasonable payments.[174] When this happens, they are paid something for the tissue itself—they capture some of its value for themselves—rather than re-gifting the value of the tissue to the ultimate recipient.[175] The U.S. "government takes almost no steps to stop intermediaries from selling tissue or (which amounts to the same thing) earning super-normal profits."[176] That is to say, tissues are routinely commodified after they are initially donated.

Yet, this is not, at bottom, a non-enforcement problem. Commodification concerns cannot be resolved simply by doing a better job of enforcing NOTA. Our intellectual property (IP) regime undermines NOTA's cap on what intermediaries may earn.[177] As

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[170] *Cf.* Katz, *The Re-Gift of Life: Who Should Capture the Value of Transplanted Human Tissue?*, 18 No. 4 HEALTH LAW. 14, 15 (2006) ("Many people stand between [tissue] donors and recipients—including tissue banks, processors, health care providers, and firms that distribute allografts to these providers.").

[171] *See supra* note 122.

[172] Siminoff, Traino, & Gordon, *supra* note 1, at 961.

[173] MICHELE GOODWIN, BLACK MARKETS: THE SUPPLY AND DEMAND OF BODY PARTS, 19 (2006).

[174] *Cf.* Katz, *supra* note 170, at 15. Nonprofit tissue banks "typically sell tissue for no more than what it costs them to procure, handle, inspect, and ship [tissue], plus earn normal profits (5-10%) for overhead, capital improvements, and the like." *Id.* For-profit tissue banks, by contrast, typically seek super-normal profits. *Id.*

[175] *Id.*

[176] *Id.*

[177] Katz, *supra* note 170, at 15.

mentioned above, some tissue processors use patented methods to process tissues and/or to make patented allografts.[178] Patent holders are given the exclusive right to an invention for a period of years and can thereby earn monopoly profits.[179] Robert Katz points out:

> After a certain point, it becomes exceedingly difficult to distinguish between: (a) the super-normal profits that NOTA prohibits intermediaries from earning for their transplantation-related activities; and (b) the unlimited profits that patent law lets patent-holders earn so as to encourage investment in socially useful innovations.[180]

Because of the manner in which donated tissues are processed and distributed, the tendency toward commodification is a natural one for tissues in a way that it is not for organs. One might even conclude that some degree of commodification is unavoidable.

Therefore, the debate over the commodification of cadaveric tissue is arguably not about commodification at all, but rather about who should capture the value of these cadaveric tissues.[181] I am not advocating for commodification of tissues. Rather, I am making the narrower claim that commodification is already occurring, in part because NOTA fails to adequately differentiate tissues from organs.

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[178] *Id.*; *see also* Buck, *supra* note 12, at 125.

[179] Katz, *supra* note 170, at 15.

[180] *Id.*

[181] *See* Mahoney, *supra* note 11, at 165; *see also* Katz, *supra* note 170, at 15 ("The most pressing normative question is not *whether* cadaveric tissue should be sold, but *who* should capture its value.").

B. Exploitation

At the most general level, exploitation occurs when one individual takes unfair advantage of another.[182] Exploitation occurs when, due to an asymmetry of bargaining power, one party to a transaction insufficiently benefits or assumes an unfair share of the burden as compared to other parties. One of the concerns behind NOTA was that living kidney donors would not get an adequate payment in the bargained for exchange—that is, that the rich would exploit the desperately poor by paying too little for their organs.[183] The solution was to ban sales.[184]

However successful NOTA's ban has been in protecting living organ donors from exploitation, it has not succeeded in avoiding the exploitation of cadaveric tissue donors. The tissue transplantation industry in the United States is worth multiple billions of dollars, and its profits are a reflection of the system of altruistic tissue donation established by NOTA.[185] Tissue processors who pursue super-normal profits capture the economic value

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[182] Alan Wertheimer & Matt Zwolinski, *Exploitation*, THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Spring 2013 Edition), Edward N. Zalta (ed.), http://plato.stanford.edu/archives/spr2013/entries/exploitation/.

[183] This concern, of course, is too simplistic, as it overlooks the possibility that the exploitation is mutually advantageous. For a discussion of mutually beneficial exploitation in organ transplants, *see* I. Glenn Cohen, *Transplant Tourism: The Ethics and Regulation of International Markets for Organs*, 41 J.L. Med. & Ethics 269, 274-277 (2013). Professor Cohen notes that "[l]abeling a transaction as mutually advantageous exploitation does not render it *per se* unproblematic, but it requires us to determine if the seller is nonetheless treated unfairly." *Id.* at 275.

Additionally, one might argue that it is unacceptably paternalistic to oppose the sale of organs because the poor would be most likely to sell their organs. I, personally, am wary of blocking transactions that would make individuals better off by their own lights—particularly if we are unwilling to take other steps to ensure that their needs are met.

[184] An alternative way to avoid exploitation would, of course, be to set a price floor rather than to set a price ceiling of zero.

[185] Patrick D. Carlson, *The 2004 Organ Donation Recovery and Improvement Act: How Congress Missed an Opportunity to Say "Yes" to Financial Incentives for Organ Donation*, 23 J. CONTEMP. HEALTH L. & POL'Y 136, 137 (2006).

of donated tissues, rather than acting as stewards of that value as it passes from the altruistic donor to the ultimate allograft recipient.[186] The selflessness of altruistic donors "makes it more difficult to come to terms" with the multibillion-dollar tissue industry[187] and could lead one reasonably to conclude that donor altruism is routinely exploited.[188]

Yet, the moral weight of such a claim is not immediately clear. Perhaps, for instance, cadaveric tissue donors—who clearly do not benefit from retaining their tissues—would prefer to donate their tissues *in spite of* the unfair distribution of financial benefits. They, or their family members who might consent to postmortem donation, may feel like they benefit sufficiently from the knowledge that they are helping others. While such a transaction may (by definition) be unfair, it should not necessarily be stopped if both parties reasonably conclude that they benefit by transacting. Outright prohibition might be overly paternalistic—in addition to being socially undesirable because of the lost benefits to tissue recipients—on this account.

While the account just provided is plausible, I do not wish to suggest that exploitation of tissue donors is necessarily unproblematic. Here, it is helpful to draw a distinction between consensual and non-consensual exploitation.[189] Although consent is required for donation, examination of informed consent practices for tissue donation

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[186] Katz, *supra* note 11, at 14.

[187] Andrew Conte & Luis Fábregas, *Gift of Life Worth Millions to Donation Organizations*, TRIBLIVE, August 21, 2013, http://triblive.com/news/allegheny/4408091-74/organ-organizations-procurement#axzz3TdNEjy5t. Conte and Fábregas quote Peter A. Clark, a medical ethics professor, as wondering "if donor families even know that these people are making money off their tissues? I don't think so . . . Where's the fairness?" *Id.*

[188] *E.g.,* Michelle Goodwin, *Altruism's Limits: Law, Capacity, and Organ Commodification*, 56 RUTGERS L. REV. 305, 395 (2004) ("The regulatory silence on payments for tissues between public and private industries and agencies blurs notions of pure altruism and exploits the unaware donor and public.").

[189] Cohen, *supra* note 183, 274. Consent should be voluntary, informed, and competent. *Id.* at 277.

suggests there are numerous shortcomings, and many family members making decisions about donation of a deceased loved one's tissue are not receiving information that might reasonably be considered material.[190] Less than half of tissue requests, for example, include information pertaining to the potential involvement of for-profit companies, or the potential use of donated tissue for cosmetic procedures.[191] Simply put, "[p]eople who donate have no idea tissue is being processed into products that per gram or per ounce are in the price range of diamonds."[192]

On the basis of this empirical evidence, I would argue that there is presently pervasive non-consensual exploitation of tissue donors, and it could even be said that some tissues are obtained fraudulently. This type of donor exploitation is deeply problematic—and it is problematic however one might feel about the permissibility of consensual, mutually beneficial exploitation. NOTA, rather than stamping out exploitation of tissue donors, has fostered it by making it possible for everyone but the donor to benefit from tissue donation.

C. Coercion (or Undue Inducement)

An oft-cited concern with allowing a market in organs is that the poor will be coerced to sell their organs to the highest bidder without regard for the health or safety of

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[190] Siminoff & Traino, *supra* note 145, at 91.

[191] *Id.* Information included in less than half of the tissue requests pertained to the processing, storage, and distribution of the donated tissue; the potential involvement of for-profit as well as not-for-profit companies, the potential use of donated tissue for cosmetic procedures. *Id.*

[192] Katches, Heisel, & Campbell, *supra* note 144 (quoting ethicist Arthur Caplan).

the donor.[193] Indeed, the design of International Kidney Exchange, Ltd. seemed calculated to provoke precisely such fears. Coercion serves as an interesting counterpoint to exploitation: the exploitation fear is that the prospective donor will be offered *too little* payment, whereas the coercion fear is that the individual will be offered *too much* payment and that said offer will be too good to refuse despite the potentially damaging consequences.[194]

Coercion is the use of a threat of harm—whether to make a person worse off than at her baseline or to violate her rights—to compel someone to do something against her will.[195] The classic example is the mugger's threat: "Your money or your life." The threat narrows an individual's options such that their only reasonable choice is to comply. Thus, coercion is not the right way to describe what happens when tissues or organs are sold.[196] Genuine offers of money (e.g., as payment for receipt of an organ) are, by definition, not threats—they expand rather than narrowing the individual's options—and therefore aren't coercive.[197]

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[193] Williams, Finley, & Rohack, *supra* note 44, at 309; *see, e.g., Flynn v. Holder*, 684 F.3d 852, 860 (9th Cir. 2012).

[194] Cohen, *supra* note 183, at 276-277. The relationship between undue inducement and exploitation has been described as a paradox: the higher the monetary benefit, the less likely exploitation is, yet, the higher the monetary benefit, the more likely that individuals are unduly influenced. *See,* Ruth Macklin, *The Paradoxical Case of Payment as Benefit to Research Subjects*, 11 IRB: ETHICS AND HUMAN RESEARCH 1, 1 (1989).

[195] *E.g.*, Anderson, Scott, "Coercion", *The Stanford Encyclopedia of Philosophy* (Summer 2015 Edition), Edward N. Zalta (ed.), forthcoming URL = <http://plato.stanford.edu/archives/sum2015/entries/coercion/> ("Most will recognize the connection of coercion with threats as a matter of common sense: armed robbers, mafias, the parents of young children, and the state all make conditional threats with the intention of reducing the eligibility of some actions, making other actions more attractive by comparison.").

[196] This is not to claim that coercion could never be a problem. Someone might, of course, be threatened with death, e.g., if they do not donate a kidney.

[197] *C.f.*, Alan Wertheimer & Franklin G. Miller, *Payment for Research Participation: a Coercive Offer?*, 34 J. MED. ETHICS 389, 391 (2008). *But see* Zimmerman, David (2002). "Taking Liberties: The Perils of 'Moralizing' Freedom and Coercion in Social Theory and Practice," *Social Theory and Practice*, 28: 577–609.

Objections regarding the effect money can have on the potential donor are more appropriately characterized as concerns about undue inducement. Undue inducement "occurs through an offer of excessive, unwanted, inappropriate or improper reward or other overture in order to obtain compliance."[198] Undue inducements are widely thought to have two concerning cognitive effects. They may impair an individual's ability to exercise proper judgment, encouraging them to engage in activities that contravene their best interests,[199] and/or prompt individuals to lie, deceive, or conceal information that, if known, would disqualify them from a particular course of action.[200] The second effect, deceit, is less concerning in the context of tissue donation because objective factors like blood tests, rather than self-report, can be used to determine donor eligibility. The first effect, however, appears to be at the heart of inappropriately labeled "coercion" concerns.

Terminology aside, the fear that individuals will be motivated by money to do something that contravenes their best interests (or the best interests of a deceased family member) is dramatically reduced when tissues are donated after death. Unlike living organ donors, whose health and well being may clearly be harmed by donation,[201] cadaveric

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[198] THE NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979).

[199] Ezekiel J. Emanuel, *Ending Concerns About Undue Inducement*, 32 J. OF LAW, MED., & ETHICS 100, 100 (2004). Philosophers Alan Wertheimer and Franklin Miller are emphatic that "[a]s a general category, an inducement is undue only when it predictably triggers *irrational* decision-making given the agent's own settled (and reasonable) values and aims. . . . Distortion of judgment is the key." Alan Wertheimer & Franklin G. Miller, *Payment for Research Participation: a Coercive Offer?*, 34 J. MED. ETHICS 389, 391 (2008).

[200] *Cf.* Ruth Macklin, *'Due' and 'Undue' Inducements: On Paying Money to Research Subjects*, 3 IRB: ETHICS AND HUMAN RESEARCH 1, 2 (1981). *See also* U.S. DEP'T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK, Chapter 3 (1993) (warning that undue inducements "may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling—or continuing—as participants in a research project"); *but see* Ezekiel J. Emanuel, *Ending Concerns About Undue Inducement*, 32 J. OF LAW, MED., & ETHICS 100, 103–104 (2004) (stating that it is unclear whether lying is a general problem).

[201] *See* Debra Budiani-Saberi & Deborah M. Golden, *Advancing Organ Donation Without Commercialization: Maintaining the Integrity of the National Organ Transplant Act*, Issue Brief, American Constitutional Society

tissue donors do not assume *health* risks by donating because they are already dead. Admittedly, cadaveric tissue donation may be inconsistent with a donor's values or with wishes and desires expressed while the donor was alive.[202] For example, "Jewish law proscribes desecration of the dead, which has been interpreted by many to mean that Judaism prohibits organ donation."[203] What, if any harm, might individuals[204] suffer if they posthumously become tissue donors in contravention of values or preferences expressed while they were alive?

It is controversial that the dead can suffer any harm at all. If one does not believe the dead can be harmed,[205] undue influence is not a concern *at all* in the context of cadaveric tissue donation. If, however, one believes that the dead can suffer harms, these are most likely to be dignitary harms.[206] One might argue that, insofar as undue inducement is the relevant concern, potential post-mortem harms to dignity are much less worrisome than potential harms to health and well-being faced by living donors. This may

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(2009) (describing an impoverished Egyptian man who sells his kidney and subsequently regrets the decision when he experiences lingering health effects); *but see* Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1813, 1841 (2007) ("Some argue that allowing organ sales would unduly pressure poor providers to put their health and lives at risk. Yet the risk is modest.") (internal citations omitted).

[202] Lior J. Strahilevitz, *The Right to Destroy*, 114 YALE L. J. 781, 823 (2005) ("In the organ donation case, religion, superstition, and aesthetic considerations may explain why someone would want his organs to decay upon his death.").

[203] Danielle Ofri, *In Israel, a New Approach to Organ Donation*, NY TIMES, February 16, 2012, http://well.blogs.nytimes.com/2012/02/16/in-israel-a-new-approach-to-organ-donation/?_r=0. Most religions, however, support organ and tissue donation as a charitable act. SEOPF/UNOS, ORGAN AND TISSUE DONATION: A REFERENCE GUIDE FOR CLERGY, 4th ed., 2000. Cooper ML, Taylor GJ, eds.

[204] Obviously, there may be broader social harms if people routinely see that the wishes of the dead are set aside to make organ and tissue donation possible. If this becomes sufficiently widespread, the living may experience some harm from anticipating that their wishes will be overridden.

[205] *E.g.*, John A. Robertson, *Paid Organ Donations and the Constitutionality of the National Organ Transplant Act*, 40 HASTINGS CONST. L.Q. 221, 272 ("At that point the deceased donor has no interests to be protected.").

[206] Strahilevitz, *supra* note 202, at 823.

be because the magnitude of the harm is smaller, the probability of the harm is lower, for example, because relatively few potential donors have deeply-held values and interests of the kind that tissue donation would contravene, or both.

The essential point is that while NOTA's drafters feared donors would make irrational choices motivated by money,[207] undue inducement appears much less likely to occur—and might not occur at all—in connection with cadaveric tissue donation.

IV. Proposal: An Act Tailored to Tissues

In 2007, Senator Chuck Schumer introduced legislation that would have established mandatory requirements for what tissue banks had to tell donor families[208] and required the Secretary of HHS to promulgate regulations defining "reasonable payments" for the purposes of NOTA.[209] The bill died after heavy lobbying by the industry.[210] In this section, I wish to argue that while Senator Schumer's legislation had merit, it did not go far enough in creating a distinct and more comprehensive regulatory structure for tissues.

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[207] Notably, a ban on offers of money is not the only way to address undue inducement. It would also be possible to limit the amount of money offered, so that it is a *mere* rather than an *undue* inducement. Or, one could implement more rigorous informed consent procedures to ensure that only those who clearly comprehended the risks of donating could do so.

[208] S. 1479 – Safe Tissue Act § 4, May 24, 2007. The would have required consent regarding "(A) the type of human cells, tissues, or cellular or tissue-based product to be donated; (B) the purpose for which such human cells, tissues, or cellular or tissue-based products shall be used, such as transplantation for medical purposes, transplantation for cosmetic purposes, therapy, research, or medical education; and (C) other matters as determined appropriate by the Secretary." Failure to comply with the model form would be subject to a civil penalty of not more than $5,000.

[209] S. 1479 – Safe Tissue Act § 6.

[210] Kate Wilson, *Abusing the 'Gift' of Tissue Donation*, www.icij.org/tissue/abusing-gift-tissue-donation (July 19, 2012).

For the reasons outlined above, tissues and organs are best understood as distinct, and there is an uncomfortable fit between the ethical concerns that motivated NOTA and the present-day realities of the tissue industry. Moreover, current regulatory frameworks have not responded sufficiently to the distinct challenges posed by tissue transplantation. My proposal is to sever tissues from NOTA and create a stand-alone tissue-specific act. Although state laws regulate tissues and organs, legislative changes should initially occur at the federal level. It is likely that once tissues are severed from NOTA, and new federal legislation changes the scheme by which tissues are donated, states will follow.

My proposal has four central elements (1) strengthening informed consent, (2) establishing a schedule of "reasonable payments," (3) permitting the sale of tissues by donors, and (4) tracking products made from human tissue.

A. Enhance Informed Consent Requirements

Informed consent is a procedural requirement intended to secure 2 core values: (1) respect for individuals' autonomy and (2) protection of individuals' well being.[211] With adequate information, tissue donors (or their surrogates) should be able "to make an informed decision and weigh their own dignitary interests against financial and altruistic interests to determine whether to donate."[212]

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[211] Emily A. Largent, David Wendler, Ezekiel J. Emanuel, and Franklin G. Miller, *Is Emergency Research without Informed Consent Justified? The Consent Substitute Model,* 170 ARCHIVES OF INTERNAL MEDICINE 668, 669.

[212] Williams, Finley, & Rohack, *supra* note 44, at 313.

Unfortunately, as discussed above, empirical evidence supports the claim that consent processes for tissue donation are often misleading.[213] Michelle Oberman has identified three problematic aspects of the present, unregulated process:

> First, the most obvious nondisclosure problem lies in the fraudulent claims made by those who assure donors that their loved one's tissue will be used for "medical" or "life-saving" purposes. . . . A broader risk of fraud lies in the problem of delineating the possible end uses of donated tissue. For instance, one might believe that cosmetic surgery is a relatively frivolous endeavor and that donors might be disinclined to make a gift of their loved ones' tissue if they knew it would be used to enhance the puffiness of someone's lips or penis. . . . A third nondisclosure concern pertains to the monetary gains associated with a tissue's use.[214]

Keeping these three non-disclosure problems in mind, tissue banks should be required to disclose the range of non-profit and for-profit intermediaries that work with donated tissue; the various ways in which intermediaries might process or distribute this tissue; and the ways in which tissue is routinely used.[215] In addition to disclosure of this material information, individuals should be given the option of deciding whether for-profit companies can use donated tissues and delimiting which uses are acceptable (e.g., yes, this donated skin can be used to treat burn victims, and no, it cannot be used for penis plumping).

Disclosure is necessary because tissue banks undoubtedly have far greater information about the commercial potential of donated tissues than do potential donors.[216]

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[213] *See supra* note 191.

[214] Oberman, *supra* note 83, at 914-915.

[215] *Id.* at 924.

[216] *Cf.* Russell Korobkin, *"No Compensation" or "Pro Compensation":* Moore v. Regents *and Default Rules for Human Tissue Donations*, 40 J. HEALTH. L. ___ ("[R]easearch scientists undoubtedly have far greater access to information concerning the legal rules governing tissue transfers and the commercial potential of biomedical research than do potential donors.")

Moreover, disclosure is consistent with existing law regarding property (or lack thereof) in the body. In *Moore v. Regents of the University of California*,[217] for example, the court refused to recognize a property interest in tissues or cells that had been removed from one's body for therapeutic purposes and chose, instead, to rely on the doctrine of informed consent.

Although HHS previously declined to adopt a mandatory disclosure rule,[218] several states already have mandatory disclosure laws. In California, for example, "[t]he revised consent form or procedure shall separately allow the donor or donor's representative to withhold consent for any of the following: (A) Donated skin to be used for cosmetic surgery purposes. (B) Donated tissue to be used for applications outside of the United States. (C) Donated tissue to be used by for-profit tissue processors and distributors. . . ."[219] Idaho requires that any person or persons . . . approached for purposes of obtaining informed consent shall be provided with "[a] statement that tissues or parts may be retrieved and/or used by for-profit procurement entities.[220] In Wisconsin, the record of the gift must include the following statement:

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[217] 793 P2d 479 (Cal 1990).

[218] In 2006, HHS issued a final rule regarding conditions for coverage for OPOs. 42 CFR Parts 413, 441, et al. Medicare and Medicaid Programs; Conditions for Coverage for Organ Procurement Organizations (OPOs); Final Rule. Although HHS initially proposed that consent contain "information (such as for-profit or non-profit status) about the organizations that will recover, process, and distribute the tissue," this parenthetical requirement was left out of the final rule. 42 C.F.R. § 486.342. HHS explained, "We believe the most appropriate course of action is to allow each OPO to determine independently what information it needs to disclose about the various organization that will be involved in the donation process. Thus, we have not finalized a requirement for OPOs to disclose the profit status of tissue banks to families of potential donors and other decision makers." Federal Register/Vol. 71, No. 104/Wednesday, May 31, 2006, at 31020.

[219] West's Ann.Cal.Health & Safety Code § 7158.3.

[220] I.C. § 39-3413A.

> I understand that donated bones or tissues, including skin, may have numerous uses, including for reconstructive and cosmetic purposes, and that multiple organizations, including nonprofit and for-profit organizations, may recover, process, or distribute the donations. I further understand that I may, by this record, limit the use of the bones or tissues, including skin, that are donated or types of organizations that recover, process, or distribute the donation.[221]

Three objections should be considered. First, some commentators have vocalized their support for legislative consent—also known as presumed consent—with the possibility of opting out as a way of addressing the severe shortage of vital organs for transplantation.[222] That is, individuals would be organ and tissue donors at the time of death *unless* they specifically stated during their lifetime that they did not wish to donate. My proposal is inherently at odds with presumed consent schemes, but this is not a problem as presumed consent schemes are untenable. Arguably, the very phrase "presumed consent" is a bit of a misnomer. It is not a type of actual consent, but signifies a situation in which there is compelling reason to believe that a given individual, if able to do so, would willingly consent to an intervention.[223] The paradigmatic case is the unconscious patient who comes to the emergency room and is treated—without explicit consent—to avoid death or severe incapacity.[224] There are not, however, good empirical grounds for claiming that even though decedents have not given consent, they would consent to organ

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[221] W.S.A. 157.06. It is also required that the person making the anatomical gift sign to acknowledge that he or she has read these sentences, or that the sentences have been read aloud to him or her. *Id.* A line or space must be provided for the person making the gift to specify a limitation, if any, on the use of bones or tissues or on the types of organizations that may recover, process, or distribute the donation. *Id.*

[222] *See, e.g.*, Linda C. Fentiman, *Organ Donation As National Service: A Proposes Federal Organ Donation Law*, 27 SUFFOLK U. L. REV. 1593 (1993). *See generally* David Orentlicher, *Presumed Consent to Organ Donation: Its Rise and Fall in the United States*, 61 Rutgers L. Rev. 295 (2009) (arguing that presumed consent reached its peak in the United States in 1990).

[223] Robert M. Veatch, *Implied, Presumed, and Waived Consent: The Relative Moral Wrongs of Under- and Over-Informing*, 7 AM. J. BIOETHICS 39, 40 (2007).

[224] *Id.*

donation if only they could be asked. Philosopher Robert Veatch asserts that "it is empirically wrong to presume consent of deceased persons to be donors of organs for transplant."[225] In 1986, the HHS Task Force on Organ Transplantation cited public opposition "as the sole basis for rejecting the presumed consent approach."[226]

Second, "some industry actors fear that publicizing the involvement of for-profit businesses in the tissue industry will discourage donations."[227] This is an empirical claim, and a plausible one.[228] In a 2010 study, researchers found that less than a quarter of families agreed or strongly agreed that it is acceptable for donated tissues to be processed and distributed by for-profit companies.[229] After the California state legislature mandated consent procedures, the number of donors who withheld consent for for-profit involvement has increased.[230] I actually see these empirical results as favoring a disclosure requirement, rather than as offering suitable grounds for objection to one. Although the

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[225] *Id. See also* Michele Goodwin, *Rethinking Legislative Consent Law?*, 5 DEPAUL J. HEALTH CARE L. 257 (2002) (discussing racial and religious reasons for rejecting presumed consent and the inadequacy of opt-out provisions).

[226] Orly Hazony, *Increasing the Supply of Cadaver Organs for Transplantation: Recognizing That the Real Problem is Psychological Not Legal*, 3 HEALTH MATRIX 219, (1993).

[227] Katz, *supra* note 11, at 945; *see also* Katches, Heisel, & Campbell, *supra* note 126 ("Industry leaders say donations would plummet if families knew their gifts generate profits."); Katz, *supra* note 170, at 16 ("One suspects that if more people knew that some processors are for-profit businesses, they would refuse to let for-profits process their donations, or refuse to donate tissue altogether. According to *The Christian Century*, a prominent Protestant journal, "[p]eople who are happy to offer their heart to save a life are not necessarily eager to donate their skin to . . . [increase] someone else's bank account.").

[228] Katches, Heisel, & Campbell, *supra* note 144 ("I thought I was donating to a nonprofit. I didn't know I was lining someone's pocket," said Sandra Shadwick of Burbank, whose brother died two years ago. Shadwick gave her brother's remains to a Los Angeles tissue bank. "It makes me angry. It makes me appalled. If it's not illegal, it ought to be. It's certainly immoral.").

[229] Siminoff, Traino, & Gordon, *supra* note 1, at 959. Only 12% of families knew that for-profit companies might sell some of the donated tissue. *Id.* at 961–962.

[230] Katz, *supra* note 11, at 958, n.92.

right to destroy one's life-enhancing tissues is questionable on welfarist grounds,[231] a reasonable person may remain sympathetic to individuals' desires to control what happens to their tissues after they die. The documented change in donor behavior following disclosure shows that for-profit involvement is *clearly* material to many. Therefore, any policy of deliberately concealing for-profit involvement raises serious ethical problems. What some might characterize as minor obfuscations of the truth for access to the social benefits that accrue from having more tissues for transplantation is a profound miscalculation.[232] Obscuring the truth surrounding tissues has the potential to damage the climate of trust not just for life-enhancing tissue donation but also for life-saving organ donation. This is a cost we cannot bear.

Finally, Michelle Oberman has suggested that "[t]hose engaged in the retrieval and processing of human tissue might object to [disclosure] regulations by arguing that they impermissibly limit free speech rights."[233] Yet, she argues that such objections are unlikely to succeed.[234] The Court has found that the government's goal of protecting the public from fraud must be balanced against charities' First Amendment rights.[235] Regulations must,

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[231] *Cf.* Lior J. Strahilevitz, *The Right to Destroy*, 114 YALE L.J. 782, 806 (2005).

[232] *Cf*. Sisslea Bok, *Shading the Truth in Seeking Informed Consent for Research Purposes*, 5 KENNEDY INSTITUTE OF ETHICS JOURNAL 1, (1995).

[233] Oberman, *supra* note 83, at 922. Oberman has stated that "[t]he informed consent paradigm is misplaced in the context of the solicitation of human tissue. There are no fiduciaries in transactions involving the solicitation of human tissue from families of the deceased. No matter how sensitively they solicit donations, OPO agents are just that--employees of the OPO. These agents are not fiduciaries for the families of the deceased. Even if their solicitations occur in the hospital, gaining a family's consent to a donation is not akin to gaining a patient's consent to treatment." Oberman, *supra* note 83, at 918. She prefers the framework of solicitation for charitable purposes. *Id.* at 918-919.

[234] *Id.* at 922.

[235] *Id*. at 922-923 (citing *Riley v. National Federation of the Blind of North Carolina, Inc.*, 487 U.S. 781, 800 (1988)).

therefore, be precisely tailored to the state's interest and must not be unduly burdensome on the right to free speech.[236] The apparently materiality of the information that I propose to disclose can be defended as consistent with state common law governing fraud—nondisclosure or partial disclosure is almost certain to mislead prospective donors, whereas disclosure enables donors to make more informed choices about whether and how to donate.[237]

B. Establish and Enforce a Schedule of "Reasonable Profits"

NOTA's exception for reasonable payments doubtlessly serves an important purpose in tissue transplantation. Functioning markets spur innovation—as mentioned above, there is an important role for IP in the tissue industry—and ensure that tissues are harvested and become available for transplantation.[238] It is, therefore, neither feasible nor desirable to prohibit money from exchanging hands when developing a new, tissue-specific act. At the other extreme, it is not desirable that the costs of transplantable tissues go entirely unregulated, as this would only serve to exacerbate the existing shortage of tissues for important but less-lucrative uses—for example, the shortage of skin grafts for burn patients—and further distort allocation in a way that favors those recipients with greater ability to pay rather than those with greater medical need. These latter concerns are rooted in respect for distributive justice.

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[236] *Id.* at 923

[237] *Id*. at 923-924.

[238] *See* Mahoney, *supra* note 11, at 185.

An additional argument can be made that, although it is perhaps counter-intuitive, the tissue industry is itself best served in the long run by avoiding a wholly unfettered market because many members of the public still find the sale of tissues unsavory. The persistent discomfort with the practice of brokering body parts clearly emerged in the debates waged after an anti-abortion group accused Planned Parenthood of selling fetal tissue for profit 2015, though that particular discourse heavily shaded by the controversy surrounding abortion.[239] Although I argued above that the concerns about commodification reflected in NOTA are misplaced with respect to tissues because commodification of tissue is a natural outgrowth of the nature of tissues, I recognize that it is improbable that hearts and minds will be changed overnight. This, then, also favors establishing a schedule of reasonable profits.

HHS should avoid either extreme—either forbidding payments or leaving transactions unregulated—and instead establish a schedule of what I would term "reasonable profits" for each tissue type.[240] Having an administratively set schedule that allows for fees as well as some level of profit in transactions involving tissues would limit the ability of the tissue processing industry to capture the economic value of tissues while also accommodating the fact that some processors have patent-protected products and

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[239] That tissue was to be used in research rather than in transplantation, but it was governed by NOTA. Planned Parenthood denied selling the tissue for profit. *See generally,* Cathy Lynn Grossman, *The Hidden Ethics Battle in the Planned Parenthood Fetal Tissue Scandal*, WASHINGTON POST, http://www.washingtonpost.com/national/religion/the-hidden-ethics-battle-in-the-planned-parenthood-fetal-tissue-scandal/2015/07/23/1186d368-3173-11e5-a879-213078d03dd3_story.html; Grady & St. Fleur, *supra* note 4, at n.p.

[240] Williams, Finley, & Rohack, *supra* note 44, at 314 n.333 (setting the price of tissue "very specifically, for example: $200 for a tendon; $500 for a heart valve; and $500 for a piece of skin measuring no more than four square inches . . . would be tedious to set up by may go the farthest towards compensating the [donor's] estate for the items being used and remedying the current inequities where tissues generate large amounts of money for tissue banks.").

processes and deserve to profit from their intellectual property.[241] In setting a price, it will be important to ensure that it does not seriously increase the cost of tissue donation,[242] which would compound existing distributive justice concerns.

C. Establish A Weak No-Compensation Default Rule

Tissue donors are critical to making the tissue industry's profits possible, and should—as a matter of equity—be able to receive compensation.[243] As part of the schedule of reasonable profits discussed above, HHS should determine specific amounts that it would be acceptable to pay to tissue donors (or, more precisely, to decedents' families). Such payments would not need to reflect the entire value of the tissue but could be characterized as a token of appreciation or donation incentive; moreover, such payments would alleviate the exploitation of donors.[244] Establishing a set rate of compensation addresses concerns that families would need to negotiate prices for tissues (i.e., parts of a

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[241] Katz, *supra* note 11, at 981.

[242] *Cf.* Cohen, *supra* note 10, at 35 ("If the [price is imposed legislatively], it must be a politically acceptable price, in the sense that it is generous enough to bring to the market those who are in the relatively price elastic portion of the supply curve, and yet not so generous as to seriously increase the cost of organ transplantation.").

[243] *Cf.* Moore v. Regents of the University of California, 793 P2d 479 (Cal 1990) (Mosk, J. dissenting) (calling it "both inequitable and immoral" that the defendants would deny Moore, whose "contribution to the venture is absolutely critical . . . any share in the proceeds."); *see also* Oberman, *supra* note 83, at 940 ("Justice and fairness [would be] further enhanced by requiring those who benefit from tissue donations, regardless of whether they are nominally structured as for-profit or nonprofit entities, to pay something for their raw material.").

[244] As discussed above, I find the non-consensual aspect of the current regime more obviously problematic than the existence of exploitation *per se*. A robust informed consent requirement addresses non-consensuality. Payment at the level I imagine may not address exploitation, but it should make the transaction fairer by allowing donors to share in the financial benefits of tissue donation/transplantation.

loved one) while grieving,[245] which would be both difficult and unseemly, and addresses the asymmetry of knowledge between donors and tissue banks and processors about the market value of tissues.

After the schedule is established, individuals can decide whether to be paid or to act as purely altruistic donors. In the context of use of tissues for research purposes, Russell Korobkin has argued for a weak default rule of no compensation.[246] He explains:

> In addition to establishing the default rule, the law must determine what amount of evidence will constitute an agreement by the parties to set their own term, or "contract around" the default. A "strong" default rule requires a clear contractual statement by the parties of a different allocation of resources before the rule is overridden. A "weak" default rule, in contrast, is one that courts will determine to have been overridden by the parties in the event of more ambiguous evidence that the parties wished a different resource allocation.

A weak no-compensation default is also appropriate when tissue is donated for transplantation. Some will demand payment regardless of the default; others will eschew payment regardless of the default. As Korobkin has pointed out, however, the preferences of a third group will be strongly shaped by the default.[247] A no-compensation default rule will reinforce social norms that favor altruism, but will not unacceptably (i.e., paternalistically) impinge on the autonomy of donors—or their surrogate decision-makers—and tissue banks to contract.

There are several potential objections to this proposal. First, by permitting donors to be paid for their tissues, some may argue that we are introducing the possibility of undue inducement. Even if payment is offered to cadaveric tissue donors, there could

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[245] *Cf.* Oberman, *supra* note 83, at 939.

[246] Korobkin, *supra* note 216.

[247] *Id.*

rarely be undue inducement. People are currently routinely asked to donate cadaveric tissues for free, and the request to donate—coupled with an offer of payment—will not change the risks or burdens associated with tissue donation.[248] If the risks are acceptable when donation is altruistic, the introduction of compensation does not somehow make them unreasonable. Of course, the offer of payment may enhance the perceived benefits of post-mortem tissue donation—and indeed, I hope it will, in order to offset the decline in tissue donation that may occur in the wake of a requirement for greater disclosure as part of the informed consent process. The offer of payment may even result in a net increase in the number of people who benefit from allografts.[249] Thus, the offer of payment would certainly be (intended as) an inducement, but that does not make it undue. Fears of undue inducement should be further allayed because, on my proposal, (1) there is a weak default rule of no compensation, meaning that not all people will receive payment and (2) payments to donors (or their families) will be set by HHS, a party external to transactions that occur between donors and processors, and will be modest. Although it is difficult, if not impossible, to draw a bright line between due and undue inducements,[250] they should be less worrisome when an offer of payment is relatively small, that is, relatively less enticing.

Second, there may be religious strictures—or other value structures—that prevent some people from selling their tissues. For example, Pope John Paul II explicitly addressed

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[248] *Cf.* Robertson, *supra* note 206, at 266 ("The risk [organ donors] are taking is not unreasonable, because altruistic donors have long assumed them without paid inducement.").

[249] Katz, *supra* note 174, at 16. In 2012, one-quarter of the population "reported that a financial incentive would make them more likely to donate their organs." HHS, HRSA, *supra* note 3, at 52.

[250] *E.g.*, Wertheimer & Miller, *supra* note 197, at 391 ("[The] distinction between an unproblematic . . . inducement and an undue inducement is not a feature of the inducement itself. It is a function of the relation between the inducement and the subject's response to it.").

the sale of tissues at the First International Congress of the Society for Organ Sharing in 1991, where he said, "[T]he human body is always a personal body, the body of a person. The body cannot be treated as a merely physical or biological entity, nor can its organs and tissues ever be used as item for sale or exchange."[251] The weak default rule of no compensation would allow people who object to payment, on whatever grounds, to donate their tissues after death. Thus, this system allows altruistic donation and compensated donation to peaceably co-exist.

Third, some may object that this is simply commodification. It is, however, incomplete commodification—something less than a laissez-faire market regime.[252] Although non-commodification may be the ideal, to achieve justice in non-ideal circumstances (such as those in which we live), we have to choose the best alternative available to us. Margaret Radin has argued, "[W]e should understand there to be a continuum reflecting degrees of commodification that will be appropriate in a given context."[253] She distinguishes two aspects of incomplete commodification: the participant aspect, which draws attention to the meaning of an interaction for those who engage in it, and the social aspect, which uses regulation to limit the choice set.[254] Tissues are a possible example of incomplete commodification. The personal importance that many of us attach to tissue donation will not be understandable entirely in monetary terms, even if we

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[251] Paolo Bruzzone, *Religious Aspects of Organ Transplantation*, 40 TRANSPLANTATION PROCEEDINGS 1064, 1064 (2008) (quoting Pope John Paul II).

[252] Radin, *supra* note 164, at 1856.

[253] *Id.* at 1918.

[254] *Id.*

demand or accept money.[255] There is a deeply personal aspect to seeing your loved one's tissues going to another. Establishing a weak no-compensation default should be seen to promote the non-market significance of tissue. Moreover, establishing a fixed price to be paid to tissue "donors" prevents this from being a bare-knuckled fight in the markets.

D. Require Tracking of Tissue Products

Tissues donated by one person may yield more than 100 tissue grafts for transplantation.[256] Although millions of patients safely receive tissue transplants each year, there are risks associated with tissue transplantation.[257] More than 50 tissue-transmitted infections have been reported in the literature since 1998, but the actual number may be higher due to "the lack of active surveillance for donor-derived infection or of an efficient means for reporting suspected infection in recipients."[258] Another obstacle to complete data is the incomplete identification of co-recipients, or the various individuals who receive transplants from a single donor.[259] Additionally, an adverse event may occur soon after transplantation or it may occur many years later, when it is less likely to be attributed to the transplant.[260]

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[255] *Cf. id.* (giving the example of a home, which has market value but also "a nonmonetizable, personal aspect").

[256] Reena Mahajan & Matthew J. Kuehnert, *How Can We Improve Tracking of Transplanted Tissue in the United States?*, 15 CELL TISSUE BANK 287, 287 (2014).

[257] DePaolo & Barbeau, *supra* note 143, at 443.

[258] Matthew J. Kuehnert, Krista L. Yorita, Robert C. Holman, D. Michael Strong, and AABB Tissue Task Force, *Human Tissue Oversight in Hospitals: An AABB Survey*, 47 Transfusion 194, 197 (2007).

[259] *Id.*

Clusters of transplant-transmitted infections—which variously resulted from deliberate misconduct,[261] error,[262] or technological inadequacy[263]—have highlighted the challenges of tracking donated tissues from an infected donor to numerous recipients.[264] Existing practices for tissue tracking "do not ensure rapid communication through the distribution chain as soon as a problem is discovered."[265] There are several reasons for this, each of which must be addressed to protect health and promote public trust.

First, there is a lack of common coding and nomenclature for tissue.[266] At present, it is left to the individual tissue bank to determine what to call each graft type it distributes.[267] By contrast, "a common coding and nomenclature . . . exists for most other healthcare products of human origin, such as blood and blood products, and it is being developed for cellular therapy products, human milk banking, ocular tissue, and other tissue types."[268] This system is known as the ISBT-128.[269] Common coding and nomenclature should be required for tissues.

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[261] DePaolo & Barbeau, *supra* note 143, at 443 (describing how "Biomedical Tissue Services Ltd. distributed tens of thousands of illegally obtained and improperly processed tissues throughout the world . . . placing thousands of tissue recipients at risk).

[262] Mahajan & Kuehnert, *supra* note 256, at 288 (describing how positive nucleic acid test results were misread as negative due to a laboratory error, resulting in an infected graft being implanted into an infant).

[263] Kuehnert et al., *supra* note 258, at 198 (describing how "[n]ew results can . . . occur when donors are retested due to advances in technology, such as advanced generations of test development").

[264] Mahajan & Kuehnert, *supra* note 256, at 288.

[265] DePaolo & Barbeau, *supra* note 143, at 444.

[266] Mahajan & Kuehnert, *supra* note 256, at 288.

[267] *Id.* ("[T]issue graft names can be proprietary, but most often the draft is simply named differently by different tissue banks (i.e. an iliac crest wedge can also be named a tricortical wedge)).

[268] *Id.*

[269] *See generally* P. Distler, *Traceability and Unique Identifiers*, 9 ISBT SCIENCE SERIES 98 (2014).

Second, tissue banks are required only to track tissue to the healthcare facility level. Notification of tissue use to the supplier by a healthcare facility (e.g., a hospital notifying a tissue processor that a heart valve it produced has been implanted in a patient) is currently voluntary, and notification rates are variable.[270] As a result, tissue banks "may be unaware of whether tissue has been implanted, stored, or discarded."[271] As tissues from a single donor are distributed more widely (and sometimes globally), investigations of potential transplant-transmitted infections are becoming increasingly complex and can require mechanisms to both traceback and traceforward tissue.[272] Investigations are particularly challenging when tracking mechanisms are inadequate.[273]

Third, within most healthcare facilities, tissue is managed in a decentralized fashion, and a standardized tracking system to the patient-level is lacking.[274] This makes it difficult to locate physicians as well as to notify and test patients if potential transmissions occurred that involved a common donor.[275] Reliable systems to share and record information about tissue products—and a requirement to use them—from producer to end-user and at all the stages in between are essential.

Fourth, tissue manufacturers are required to report serious communicable disease related adverse events to FDA; however, surveillance is fundamentally passive, relying on

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[270] *Id.*

[271] Mahajan & Kuehnert, *supra* note 256, at 288.

[272] Kuehnert et al., *supra* note 258, at 197.

[273] *Id*.

[274] Mahajan & Kuehnert, *supra* note 256, at 289.

[275] *Id.*

physicians to recognize and report allograft-related infections.[276] Providers should be mandated to report adverse events if they suspect a transmission-related event.

Changes to enhance patient safety will require addressing a lack of infrastructure for tissue traceability that exists in most healthcare facilities.[277] This may increase the cost of tissue transplantation for the industry and for recipients, but are nonetheless worthwhile given the safety implications.

Conclusion

I have argued that, although NOTA does not distinguish between tissues and organs, tissues and organs are meaningfully different. I advocate crafting a new regulatory scheme for donated cadaveric tissues that (1) emphasizes greater disclosure of industry practices as part of the informed consent process to promote respect for autonomy; (2) establishes a schedule of reasonable profits to make sure that tissue banks and processors are not capturing the full value of tissues, thereby reducing commodification concerns; (3) introduces a weak no compensation default rule that allows donors to sell their tissues to reduce exploitation of altruistic donors; and (4) requires improved tracking of products made from human tissue to promote patient safety.

An advantage of this proposal is that tissues can be severed from NOTA, while leaving NOTA—and the ethically motivated scheme it established for donation and transplantation of organs—substantially intact. However, acceptance of this proposal is

[276] Sanjaya Dhakal, Dale R. Bruwen, Laura L. Polakowski, Craig E. Zinderman, & Robert P. Wise, *Assessment of Tissue Allograft Safety Monitoring with Administrative Healthcare Databases: A Pilot Project Using Medicare Data*, 15 Cell Tissue Banking 75, 76 (2014).

[277] Mahajan & Kuehnert, *supra* note 256, at 289.

not inconsistent with also holding the view that a regulated market for organs is desirable and that the ethical concerns animating the passage of NOTA in 1984 are no longer valid with respect to organs. The Institute of Medicine (IOM) published a report in 2006, ORGAN DONATION: OPPORTUNITIES FOR ACTION, in which it stated: "There are powerful reasons to preserve the idea that organs are donated rather than sold."[278] Yet, this idea is increasingly coming under attack. Even if one thinks that NOTA should be substantially revised, it will be desirable to have a tissue-specific act given the differences between tissues and organs outlined above. A second advantage of this proposal is that a tissue-specific act could be expanded to accommodate living as well as cadaveric tissue donors, as well as fetal tissue donations, and this idea merits further consideration.

[278] COMMITTEE ON INCREASING RATES OF ORGAN DONATION, INSTITUTE OF MEDICINE (IOM), ORGAN DONATION: OPPORTUNITIES FOR ACTION 15 (James F. Childress & Catharyn T. Liverman, eds., 2006).

REGULATORY UNCERTAINTY, CONCEPTUAL CONFUSION, AND A PATH FORWARD ON OFFERS OF PAYMENT TO RESEARCH PARTICIPANTS

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In the early days of 2016, news broke that six men had been hospitalized—one of whom was pronounced brain-dead—after a "serious accident" occurred in the course of a drug trial conducted in France.[1] The men were all participants in a Phase I, or first-in-human, trial of BIA 10-2474,[2] a novel compound designed to treat "anxiety and motor disorders associated with Parkinson's disease, and chronic pain in people with cancer and other conditions."[3] Each participant had been paid €1,900 (about $2,060), "including travel expenses; in return, they agreed to stay at [the testing] facility in Rennes [France] for 2 weeks, swallow a drug on 10 consecutive days, undergo extensive medical tests, and provide at least 40 blood samples."[4] The amount of payment was widely reported in the wake of the tragedy, with the implication that the offer of payment, or the amount of payment, signaled that the trial itself was ethically questionable.

Clearly, something went terribly wrong in France.[5] Yet, if we focus on what was known at the time the offer of payment was made, rather than allowing retrospective judgments and suspicions about pecuniary incentives to cloud our ethical evaluations, was it acceptable to offer the research participants €1,900? And if it was not, why not?

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[1] Sewell Chan, *6 Hospitalized, One of Them Brain-Dead, After Drug Trial in France*, THE NEW YORK TIMES (Jan. 15, 2016), http://www.nytimes.com/2016/01/16/world/europe/french-drug-trial-hospitalization.html?smprod=nytcore-ipad&smid=nytcore-ipad-share&_r=0 (last visited Feb. 1, 2016).

[2] John Brosky & Cormac Sheridan, *Six Hospitalized in Bial Clinical Trial in France*, BIOWORLD, http://www.bioworld.com/content/six-hospitalized-bial-clinical-trial-france-0 (last visited Feb. 1, 2016).

[3] Decian Butler & Ewen Callaway, *Scientists in the Dark After French Clinical Trial Proves Fatal*, 529 NATURE 263, 263 (2016).

[4] Martin Enserink, *More Details Emerge on Fateful French Drug Trial*, Science (Jan. 16, 2016), http://www.sciencemag.org/news/2016/01/more-details-emerge-fateful-french-drug-trial (last visited Feb. 1, 2016).

[5] Decian Butler & Ewen Callaway, *Researchers Question Design of Fatal French Clinical Trial*, NATURE (Jan. 22, 2016), http://www.nature.com/news/researchers-question-design-of-fatal-french-clinical-trial-1.19221 (last visited Feb. 1, 2016).

Offers of payment made to research participants[6] have been described as "one of the most contentious issues that IRBs [(institutional review boards)] deal with on a regular basis."[7] The U.S. federal regulations and the leading international codes of research ethics require that consent to participation in research be obtained in a manner that is free of coercion and undue influence (a term used interchangeably with undue inducement). Offers of payment made to research participants have been linked to both concepts, and yet the various laws, regulations, and ethical guidelines that govern the conduct of human subjects research offer relatively little in the way of specific guidance about what factors or features render offers of payment ethically acceptable, or not—or even how to define coercion and undue inducement. Therefore, IRBs—the administrative bodies "established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which [the IRB is] affiliated"[8]—and investigators are left largely without a compass to determine whether any particular offer of payment is appropriate.

Given the lack of clear regulatory guidance, one would fully expect the space inhabited by IRBs and investigators to be characterized by confusion coupled with a general trend toward conservative approaches to offers of payment—better to be safe than sorry in the midst of uncertainty. To the extent that IRBs and investigators are identifying

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[6] We prefer and will use the term "research participant" rather than "research subject." While "subject" is the more traditional of the two terms, over the past several decades, there has been a shift to using "participant" because many see it as more respectful. There continues, however, to be debate. *See* Ali Hall, *What's in a name? Research "participant" versus research "subject"*, http://primr.blogspot.com/2014/01/whats-in-name-research-participant.html (last visited Jan. 12, 2016).

[7] Bruce G. Gordon, Joseph Brown, Christopher Kratochvil, & Ernest D. Prentice, *Paying Research Subjects*, in INSTITUTIONAL REVIEW BOARD: MANAGEMENT AND FUNCTION (eds. Robery J. Amdur & Elizabeth A. Bankert) (2002).

[8] H.H.S. DEP'T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993).

legitimate ethical concerns about payment, such conservatism is appropriately protective of research participants. On the other hand, if ethical concerns about payment are overestimated (or simply wrong), the limits that follow from a conservative approach are not only unnecessary to protect research participants, but could actually be ethically inappropriate to the extent that they prevent research participants from receiving offers of payment that would fairly compensate them for the risks and burdens of their participation. Unnecessarily conservative approaches to payment might also hinder trial recruitment,[9] thereby delaying scientific and medical progress and/or unethically exposing research participants to risks and burdens that cannot be justified by their scientific value if studies fail to complete.[10] That is to say, there are potential practical and ethical costs to the confusion experienced by IRBs and investigators, and the "better safe than sorry" approach is not necessarily safer at all.

This is the first law review article to examine systematically the legal and ethical dimensions of offering payment to research participants. It argues that concerns about offers of payment in this context are attributable to misguided "research exceptionalism"—simply put, the idea that research is meaningfully different from other contexts in which individuals assume risk. As we show, the rejection of research exceptionalism with respect to payment helps settle open debates within the research ethics community about both how best to define coercion and undue inducement and how to understand their relation to

[9] *See generally*, Jeffrey L. Probstfield & Robert L. Frye, *Strategies for Recruitment and Retention of Participants in Clinical Trials*, 306 JAMA 1798 (2011); Darlene R. Kitterman, Steven K. Cheng, David M. Dilts, & Eric S. Orwoll, *The Prevalence and Economic Impact of Low-Enrolling Clinical Studies at an Academic Medical Center*, 86 ACAD MED. 1360 (2011).

[10] Scott D. Halpern, Jason H.T. Karlawish, & Jesse A. Berlin, *The Continuing Unethical Conduct of Underpowered Clinical Trials*, 288 JAMA 358, 358 (2002).

offers of payment. Recognition that research exceptionalism is problematic, coupled with the adoption of our preferred definitions of coercion and undue inducement, should resolve the confusion exhibited by IRBs and investigators with regard to offers of payment for research participation. Moreover, it should allow IRBs and investigators—two groups that have traditionally focused on whether offers of payment are too high—to focus on the more ethically salient question: are research participants being paid *enough*? We think the answer to that question is often "No."

The article proceeds as follows: Part I provides background on why payment is sometimes considered ethically problematic, and reviews the existing literature on offers of payment made to research participants. Such offers are a pervasive feature of research involving both "healthy volunteers" and "patient volunteers," individuals who have the disease or condition under study. Moreover, offers of payment span the spectrum of studies from those that pose minimal risk to participants to those that are far riskier and more burdensome. The relative frequency with which payment is offered means that investigators who design payment schedules and the IRBs that review those payment schedules routinely confront questions about the ethical acceptability of payment.

Part II surveys regulations and guidelines on the ethics of biomedical research at two levels: national and international. First, we briefly describe the U.S. federal regulations and relevant guidance documents governing human subjects research from both the Office of Human Research Protections (OHRP) within the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA). Next, we examine international guidelines, which are highly influential and may be formally (or even legally) applicable, depending on where research is conducted. Treatment of payment within

these regulations and guidelines is highly uneven: some fail altogether to address offers of payment, while others address the purpose, amount, mechanism, and timing of offers of payment, albeit in a fairly high-level way. As a result, IRBs and investigators bear significant responsibility both for determining what the terms coercion and undue influence mean in the context of offers of payment and for correctly identifying and addressing those ethical concerns when they see them. While we concede that discretion will always be needed to determine whether coercion and undue inducement are present in particular circumstances, the lack of clear definitions and guidance can lead to unnecessary confusion and conservative approaches.

In Part III, we consider a potential explanation for the debate surrounding offers of payment to research participants: research exceptionalism. Research exceptionalism is the view that biomedical research is meaningfully different from other contexts in which individuals assume risk. Although many individuals implicitly endorse the idea that research is different, we suggest that nine common justifications for research exceptionalism ultimately fail, at least when it comes to offers of payment. Though we favor robust regulatory protections for participants in human subjects research, we maintain that common arguments for research exceptionalism do not identify characteristics of research that can justify regulating offers to payment to research participants more heavily than offers of payment made in other areas.

Part IV explores the considerable academic discussion related to coercion and undue inducement in the context of research ethics generally and in relation to payment specifically. No clear consensus has materialized regarding what these concepts mean, but we review the dominant themes and arguments that have emerged. We argue for our

preferred definitions of coercion and undue inducement and show that some definitions necessarily fall with the rejection of research exceptionalism.

To demonstrate how the regulatory underdevelopment and conceptual confusion play out in practice, Part V reviews selected institutional policies related to payment of research participants. Such policies, typically promulgated by IRBs in conjunction with administrators, guide both investigators' design of and IRBs' deliberations regarding offers of payment to research participants. The want of substantive direction from either regulatory authorities or international bodies has unsurprisingly resulted in correspondingly wide variation in institutional policy.

In Part V, we also present the results of two small pilot surveys we conducted with a convenience sample of IRB members, administrators, investigators, and study coordinators. Our aim was to examine how individuals who are actively engaged in human subjects research and protection think about offers of payment generally, and about the concepts of coercion and undue inducement specifically. While these are preliminary findings, and we call for more research, our data contribute to the growing empirical literature showing that confusion exists among IRB members regarding how to define the terms coercion and undue inducement.[11] Our pilot survey is the first to examine how investigators define those terms; it is unsurprising but valuable to see that investigators are confused in much the same way that IRB members are. Moreover, both groups

[11] Emily A. Largent, Christine Grady, Franklin G. Miller, & Alan Wertheimer, *Money, Coercion, and Undue Inducement: A Survey of Attitudes About Payments to Research Participants*, 34 No. 1 IRB: ETHICS AND HUMAN RESEARCH 1 (2012). Robert Klitzman, *How IRBs View and Make Decisions About Coercion and Undue Influence*, J. MED. ETHICS (2012).

subscribe to definitions that are consistent with research exceptionalism, and inconsistent with our preferred approaches.

Finally, Part VI builds on our analysis, definitions, and findings to make recommendations for policy and practice. We recognize that it may be impossible for IRBs and investigators to reach consensus amongst themselves on what the terms coercion and undue inducement mean, given the relative ambiguity of U.S. federal regulations and international guidelines and the persistent lack of agreement among bioethicists about the features of ethically acceptable offers of payment. In the short-term, it is desirable that IRB members and investigators stop assuming that labels—coercion or undue influence—alone do sufficient explanatory work when deciding whether a payment is ethically acceptable. In the long-term, we believe that official regulatory guidance and educational efforts by enforcement agencies are needed to clarify these concepts.

Helping the research community speak with greater precision about their concerns regarding offers of payment by adoption of common definitions will enable a more concrete separation of ethically acceptable and unacceptable payment structures, which may have the effect of improving trial recruitment and promoting fair compensation of research participants, with new attention paid to the problem of underpayment.

I. Background: Offers of Payment in Biomedical Research

Human subjects research is research in which human beings ("as opposed to animals, atoms, or asteroids"[12]) are the subjects of study. A "human subject" is defined by

[12] David Wendler, *The Ethics of Clinical Research*, THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Fall 2012 Edition), Edward N. Zalta (ed.), http://plato.stanford.edu/archives/fall2012/entries/clinical-research/.

the regulations governing most federally-funded human subjects research as "a living individual about whom an investigator . . . conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information."[13] Clinical research is that "subset of human subjects research which focuses on improving human health and well-being."[14] Clinical research is "designed to test an hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge . . . . Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective."[15]

The phrase "offer of payment" is an umbrella term used to capture all instances in which money—either cash or cash equivalent—is provided to research participants. Although controversy persists surrounding offers of payment to research participants, the practice is widespread and growing.[16]

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[13] 45 CFR § 46,102(f) (2005). The Notice of Proposed Rulemaking (NPRM), proposing changes to Common Rule and released in September 2015, would expand the Common Rule's definition of "human subject" to include a "living individual about whom an investigator . . . (iii) obtains, uses, studies, or analyzes biospecimens" so that it covers all research use of biospecimens, regardless of whether the biospecimens are or are not identifiable. §__.102(e)(1). *See also,* 21 CFR § 50.3(6) ("*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.").

[14] Wendler, *supra* note 12, at n.p. Social behavioral research studies individuals' responses to internal and external stimuli. While social-behavioral research is not the focus of this paper, payment is often used in that research as well. Many of the concerns raised herein would also be relevant in that context. *See also*, 21 CFR § 50.3(c) ("*Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.").

[15] Wendler, *supra* note 12, at n.p.

[16] *See*, *e.g.*, Dickert & Grady, *supra* note 34, at 198. *See also*, Christine Grady, Neal Dickert, Tom Jawetz, Gary Gensler, & Ezekiel Emanuel, *An Analysis of U.S. Practices of Paying Research Participants*, 26 CONTEMPORARY CLINICAL TRIALS 365, 366 (2005); Christine Grady, *Money for Research Participation: Does It Jeopardize Informed Consent?*, 1 AM. J. OF BIOETHICS 40, 40 (2001).

A. Why Might Offers of Payment Be Ethically Concerning?

The practice of offering payment to individuals in exchange for their participation in certain types of clinical studies is generally recognized as an important—and often essential—tool to reach enrollment targets.[17] Despite the longstanding nature of the practice, whether payment is a "necessary evil" or legitimate compensation for services rendered is the source of substantial debate. A minority of commentators contends that altruism should be the sole motivation for research participation, such that payment beyond reimbursement of a participant's out-of-pocket costs is ethically inappropriate.[18] The majority of academic literature on this topic, however, has focused on establishing those circumstances under which offers of payment may be ethically acceptable, addressing concerns related to the amount, mechanism, timing, and context of payment. [19]

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[17] Leah E. Hutt, *Paying Research Subjects: Historical Considerations*, 12 HEALTH L. REV. 16, 16 (2003). Offers of payment to research participants are often defended on the pragmatic grounds that they facilitate timely recruitment of the right numbers and types of participants. *E.g.*, Laura B. Dunn & Nora E. Gordon, *Improving Informed Consent and Enhancing Recruitment for Research by Understanding Economic Behavior*, 293 JAMA 609 (2005). While there is a need for more empirical research to show how increasing incentives affects recruitment for clinical trials specifically, there is evidence from survey research that larger offers of payment improve recruitment. *E.g.*, Nancy L. Keating, Alan M. Zaslavsky, Judy Goldstein, Dee W. West, and John Z. Ayanian, *Randomized Trial of $20 Versus $50 Incentives to Increase Physician Survey Responses*, 46 MEDICAL CARE 878 (2008); Connie M. Ulrich, Marion Danis, Deloris Koziol, Elizabeth Garrett-Mayer, Ryan Hubbard, & Christine Grady, *Does It Pay to Pay? A Randomized Trial of Prepaid Financial Incentives and Lottery Incentives in Surveys of Nonphysician Healthcare Professionals*, 54 NURSING RESEARCH 178 (2005); Scott D. Halpern, Peter A. Ubel, Jesse A. Berlin, & David A. Asch, *Randomized Trial of $5 Versus $10 Monetary Incentives, Envelope Size, and Candy to Increase Physician Response Rates to Mailed Questionnaires*, 40 MEDICAL CARE 834 (2002); David A. Asch, Nicholas A. Christakis, & Peter A. Ubel, *Conducting Physician Mail Surveys on a Limited Budget: A Randomized Trial Comparing $2 Bill versus $5 Bill Incentives*, 36 MEDICAL CARE 95 (1998).

[18] *E.g.*, Tod Chambers, *Participation as Commodity, Participation as Gift*, 1 AM. J. BIOETHICS 48 (2001).

[19] *See generally*, Carl Elliott & Roberto Abadie, *Exploiting a Research Underclass in Phase 1 Clinical Trials*, 358 NEJM 2316 (2008); Ezekiel J. Emanuel, *Undue Inducement: Nonsense on Stilts?*, 5 AM. J. BIOETHICS 9 (2006); Ruth W. Grant & Jeremy Sugarman, *Ethics in Human Subjects Research: Do Incentives Matter?*, 29 J. MED. & PHIL. 717 (2004); Trudo Lemmens & Carl Elliott, *Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects*, 7 ACCOUNTABILITY IN RESEARCH 3 (1999). In addition to broad concerns about offers of payment to research participants, unique ethical concerns also arise with respect to particular sub-populations of participants, for

As mentioned above, and as will be discussed at greater length in Part II, the U.S. federal regulations, as well as the leading international codes of research ethics, explicitly stipulate that consent to participation in research should be obtained in a manner that is free of both coercion and undue inducement.[20] Informed consent, central to ethical clinical research, serves to ensure not only that individuals control whether or not they enroll in clinical research, but also that they participate only when doing so is consistent with their values and interests.[21] In order to provide adequate informed consent, prospective research participants must be: (1) *informed* of the purpose, methods, risks, benefits, and alternatives to research participation; (2) *comprehend* this information and understand its particular relevance to them; and (3) make a *voluntary* decision to participate.[22]

Unfortunately, there is no broad consensus in the research ethics literature as to what constitutes coercion or undue inducement—a matter we delve into at length in Parts II and IV. Therefore, we will not define the terms here, instead reserving that discussion for later. There is, however, general consensus that coercion and undue inducement

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example, drug users. *See, e.g.*, Craig L. Fry, Wayne Hall, Alison Ritter, & Rebecca Jenkinson, *The Ethics of Paying Drug Users Who Participate in Research: A Review and Practical Recommendations*, 1 J. EMPIRICAL RESEARCH ON HUM. RESEARCH ETHICS 21 (2006).

[20] *E.g.*, 45 CFR 46. *See also, e.g.*, WORLD MEDICAL ASSOCIATION (WMA), DECLARATION OF HELSINKI - ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2013) ("Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who . . . may be vulnerable to coercion or undue influence."); COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ("Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.").

[21] Ezekiel J. Emanuel, David Wendler, & Christine Grady, *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2706 (2000).

[22] *See generally* J.W. BERG, PAUL S. APPLEBAUM, CHARLES W. LIDZ, AND L. PARKER, INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE (2001).

render consent invalid, though the mechanism by which they do so remains open to debate. Many understand both coercion and undue inducement to compromise voluntariness,[23] while others argue that coercion compromises voluntariness whereas undue inducement compromises comprehension.[24]

The potential effect of offers of payment on research participants has been described as either coercive, unduly influential, or both, and therefore potentially problematic in terms of satisfying the ethical (and legal) requirement for valid informed consent. Simply put, many think that the offer of money can hold an overwhelming allure for research participants, the result of which is to render invalid their consent to research participation. To pick but one example, a writer discussing the adverse events in the BIA 10-2474 trial described at the outset of this article stated that "[w]ith many in poverty, there is an inherent coercion in this type of trial" and concluded that it is "imperative . . . that we . . . minimize the coercion of financial incentives" in clinical research.[25]

Because people have highly disparate views on the necessary and sufficient conditions for coercion and undue inducement, there is great heterogeneity regarding when offers of payment are thought to be acceptable. To fully appreciate the controversy engendered by offers of payment, it is necessary to consider them at a more granular level. Various characteristics of both the payment itself and the study for which payment is being

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[23] *E.g.,* David Casarett, Jason Karlawish, & David A. Asch, *Paying Hypertension Research Subjects: Fair Compensation or Undue Inducement?*, 17 J. GEN. INTERN. MED. 651, 651 (2002) ("Undue inducements decrease voluntariness, an essential component of valid consent.").

[24] *E.g.*, Emily Largent, Christine Grady, Franklin G. Miller, & Alan Wertheimer, *Misconceptions About Coercion and Undue Influence: Reflections on the Views of IRB Members*, 27 BIOETHICS 500, 507 (2013) (arguing that coercion compromises voluntariness, whereas undue influence compromises comprehension of risks).

[25] Judy Stone, *Bial's Clinical Trial in France Ends in Disaster. What Went Wrong?*, FORBES (Jan. 16, 2016), http://www.forbes.com/sites/judystone/2016/01/16/bials-french-clinicial-trial-ends-in-disaster-what-went-wrong/#6a59c2f49b2c (last viewed Feb. 1, 2016).

offered are thought to have normative importance when determining the ethical acceptability of an offer of payment. That is what we turn to next.

B. Which Research Participants Receive Offers of Payment?

From an investigator's perspective, research participants are selected through the development of inclusion and exclusion criteria, as well as through recruitment strategies.[26] Inclusion and exclusion criteria are standards prospectively set forth in a study protocol that are used to determine whether an individual is or is not eligible to participate in a particular study.[27] Although inclusion and exclusion vary widely by study, a basic and fundamental distinction can be drawn between research participants who are healthy volunteers—individuals with no known health problems—and those who are patient volunteers—individuals at risk for or with the condition under study. Presently, demand for research participants often outstrips the number of individuals willing to take part.[28]

From a potential research participant's perspective, diverse factors may prompt agreement to participate in clinical research.[29] For instance, healthy volunteers may be

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[26] Emanuel, Wendler, & Grady, *supra* note 21, at 2704 (discussing the ethical importance of fair subject selection).

[27] Whereas inclusion criteria are characteristics that individuals must have in order to participate, exclusion criteria are characteristics the possession of which disqualifies an individual. *See generally,* Harriette G.C. Van Spall, Andrew Toren, Alex Kiss, & Robert A. Fowler, *Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medicine Journals: A Systematic Sampling Review*, 297 JAMA 1233, 1233 (2007).

[28] Dinora Dominguez, Mandy Jawara, Nicole Martino, Ninet Sinaii, & Christine Grady, *Commonly Performed Procedures in Clinical Research: A Benchmark for Payment*, 33 CONTEMPORARY CLINICAL TRIALS 860, 860 (2012).

[29] *See, e.g.*, Leanne Stunkel & Christine Grady, *More Than Money: A Review of the Literature Examining Healthy Volunteer Motivations*, 32 CONTEMPORARY CLINICAL TRIALS 342 (2011).

motivated by a wish to help others, to move science forward, or to receive financial compensation.[30] Patient volunteers may be motivated by each of these factors as well, but they may also wish to receive innovative therapies only available in the research context in hopes that they will receive direct medical benefit. A direct benefit to research participants is a benefit that arises from receiving the intervention being studied, as opposed to other types of so-called collateral benefits that may be associated with trial participation, such as access to specialists and more attentive care.[31]

There is a common perception "that money is offered only to healthy subjects in research, and rarely to patient-subjects with the disease or condition under study."[32] Relatedly, commentators sometimes assume (or argue) that while it is legitimate to offer payment to healthy volunteers for their participation in research, one should not offer to pay patient volunteers, at least when they stand to accrue other benefits from research participation.[33] Others, however, have persuasively argued that there is no inherent reason to treat healthy volunteers and patient volunteers differently with respect to payment.[34] Data suggest that, in practice, researchers do in fact nearly always offer payment to healthy

[30] *E.g.*, Luis Almeida, Benedita Azevedo, Teresa Nunes, Manuel Vaz-da-Silva, Patrício Soares-da-Silva, *Why Healthy Subjects Volunteer for Phase I Studies and How They Perceive Their Participation?*, 63 EUR. J. PHARMACOL. 1085 (2007) (finding financial reward was the most important motivation).

[31] Nancy M.P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 JL MED. & ETHICS 332 (2000).

[32] Grady, Dickert, Jawetz, Gensler, & Emanuel, *supra* note 16, at 366.

[33] *E.g.*, Trudo Lemmens & Carl Elliott, *Justice for the Professional Guinea Pig*, 1 Am. J. Bioethics 51, 52 (2001). *But see,* Dickert & Grady, *supra* note 34, at 198.

[34] Neal Dickert & Christine Grady, *What's the Price of a Research Subject? Approaches to Payment for Research Participation*, 341 NEW ENGLAND J. OF MEDICINE 198, 198 (1999).

research participants, and also increasingly offer payment to patients who participate in clinical research, even when the study holds the prospect of direct medical benefit.[35]

C. Why Are Offers of Payment Made to Research Participants?

Investigators may be motivated to offer payment to research participants for a number of reasons. See Figure 1. First, money might be offered to *reimburse* participants for research-related expenses, for example, travel to the study site. Such offers may enable individuals who could not otherwise afford to participate or who would not be willing to make a financial sacrifice to participate to do so.[36] The practice of offering money as reimbursement is uncontroversial and widely accepted.[37]

[35] Christine Grady, *Payment of Clinical Research Subjects*, 115 J. OF CLINICAL INVESTIGATION 1681, 1681 (2005). Grady, Dickert, Jawetz, Gensler, & Emanuel, *supra* note 16, at 372.

[36] Emanuel, Wendler, & Grady, *supra* note 21, at 1682.

[37] Largent, Grady, Miller, & Wertheimer, *supra* note 11, at 5.

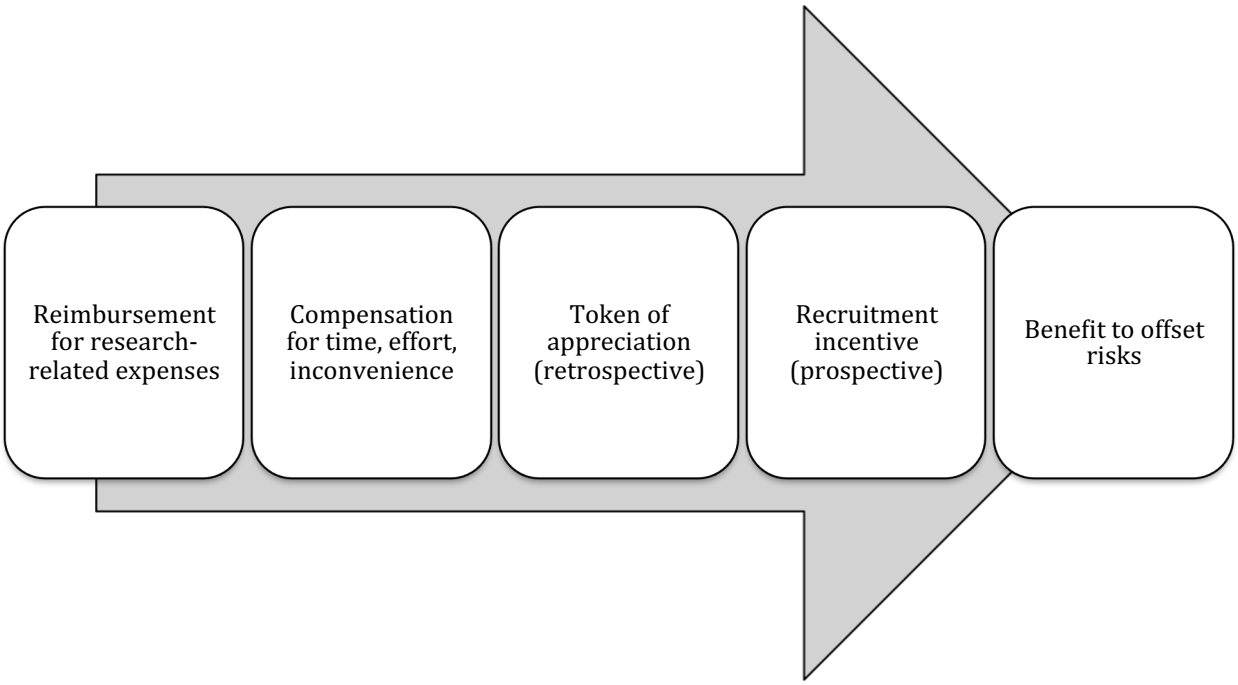

Figure 1. Reasons for Offering Payment to Research Participants, arrayed from least to most controversial.

The perceived ethical acceptability of additional reasons for offering payment, however, varies greatly.[38] Money may *compensate* individuals for time and effort expended or inconvenience experienced in the course of participating in research. Money can serve as a recruitment *incentive*, particularly if the amount offered is high enough to overcome lack of interest, or—for certain subgroups within the population—lack of awareness or distrust.[39] Payment also may be offered as a *token of appreciation*; in contrast to an incentive, which is offered prospectively, and in contrast to compensation, which aims to match the value of what has been given, a token of appreciation is generally small and

[38] *Id.*

[39] Grady, *supra* note 35, at 1682.

offered only after the decision to participate has already been made.[40] Finally, money could be viewed as a *benefit* to research participants in assessing whether the risks of participation are reasonable in comparison to the benefits,[41] although this is extremely controversial since it could allow even very risky research to proceed so long as the "price" was right.[42]

D. How Much Payment is Offered to Research Participants?

Published journal articles rarely mention whether payment was offered to research participants, and almost never mention the amount.[43] Additionally, most research studies do not specify a dollar value for any given procedure in either the protocol or consent document.[44] Yet, some efforts have been made to quantify what research participants are paid. In 2012, ethicists at the National Institutes of Health (NIH) Clinical Center reviewed

[40] Grant & Sugarman, *supra* note 19, at 735 n.3 (2004) ("[I]n the research context, providing a benefit after the decision to participate has been made is a gift or a token of appreciation, not an incentive properly speaking because the benefit does not serve as a motivator.").

[41] Alan Wertheimer, *Is Payment a Benefit?*, 27 BIOETHICS 105, 105 (2013).

[42] At present, IRBs are not permitted by OHRP to take this approach. HHS, *What does it mean to minimize the possibility of coercion or undue influence?*, U.S. OFFICE OF HUMAN RESEARCH PROTECTIONS, http://answers.hhs.gov/ohrp/categories/1566 ("IRBs should not consider remuneration as a way of offsetting risks" when deciding whether or not to approve research."). Holly Fernandez Lynch, *Human Research Subjects as Human Research Workers*, 14 YALE J. HEALTH POL L & ETHICS 122, 156–157 (2014) ("Although technically silent on the matter of whether payment to subjects may be based on risk, the [U.S. federal] regulations' direction to avoid undue inducement is often taken to mean that risk-based payment is impermissible."). While there are limits on what IRBs are allowed to consider when approving a study, there are no limits on how prospective research participants might view or perceive the offer of payment when deciding whether or not to participate.

[43] Robert Klitzman, Ilene Albala, Joseph Siragusa, Kristen N. Nelson, & Paul S. Appelbaum, *The Reporting of Monetary Compensation in Research Articles*, 2 J. EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS 61, 64 (2007).

[44] Christine Grady, *Payment of Clinical Research Subjects*, 115 J. OF CLINICAL INVESTIGATION 1681, 1681 (2005); Grady, Dickert, Jawetz, Gensler, & Emanuel, *supra* note 16, at 369.

four years of data to estimate payment amounts for common research procedures.[45] They estimated $20 for a blood sample, $10 for a urine sample, and $30 for a 1-hour questionnaire.[46] This is generally consistent with data from a national survey conducted by Elizabeth Ripley and colleagues,[47] as well as with suggested monetary compensation for routine research procedures outlined by the Boston-based Partners Healthcare Human Research Protection Program.[48] Others have found that the procedure-related dollar value for MRIs can range from $25 to $120 (mean $58) and that variation can occur even within the same institution.[49]

While these are valuable benchmarks, they hardly exhaust the spectrum of offers of payment—particularly as studies vary with respect to complexity, number of procedures, length, et cetera.[50] One study of consent documents for thirteen HIV cure studies found a range from "no payment to nearly $2,000," though neither the median nor mean payment was identified.[51] In 2005, a review of IRB-approved protocols and consent forms from 467 studies offering payment to research subjects approved by eleven IRBs across the United States found that the total amount of compensation offered for a complete study varied

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[45] Dinora Dominguez, Mandy Jawara, Nicole Martino, Ninet Sinaii, & Christine Grady, *Commonly Performed Procedures in Clinical Research: A Benchmark for Payment*, 33 CONTEMPORARY CLINICAL TRIALS 860, 867 (2012).

[46] *Id.*

[47] Elizabeth Ripley, Francis Macrina, Monkia Markowitz, & Chris Gennings, *Why Do We Pay? A National Survey of Investigators and IRB Chairpersons*, 5 J EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS 43, 54 (2010).

[48] Partners Human Research Committee, *Remuneration for Research Subjects*, http://navigator.partners.org/ClinicalResearch/Remuneration_for_Research_Subjects.pdf.

[49] Grady, Dickert, Jawetz, Gensler, & Emanuel, *supra* note 16, at 369.

[50] Our work focused on offers of payment to adults, but for data on offers of payment to adolescents, *see, e.g.*, Dina L.G. Borzekowski, Vaughn I. Rickert, Lisa Ipp, & J. Dennis Fortenberry, *At What Price? The Current State of Subject Payment in Adolescent Research*, 33 J. ADOLESCENT HEALTH 378 (2003).

[51] Gail E. Henderson, *The Ethics of HIV "Cure" Research: What Can We Learn from Consent Forms?*. 31 AIDS RESEARCH AND HUMAN RETROVIRUSES 56, 60 (2015).

from $5 to $2,000.[52] The authors found that nearly two-thirds of studies offered less than $250, and the median total across all studies was $155.[53] Interestingly, studies with some prospect of direct medical benefit, studies having at least one invasive procedure, and studies with a greater number of clinic visits were associated with higher dollar amounts offered.[54] Considered together, these figures suggest that the offer of payment made to participants in the French experiment discussed at the beginning of this paper is on the higher end of the spectrum, but certainly not off the charts.[55]

II. Regulations and Guidelines Related to Payment of Research Participants

With this background in mind, we now turn to regulations and guidelines governing human subjects research to describe what they say about coercion and undue inducement generally and what, if anything, they say about offers of payment specifically. In short, the answer is not much. The want of meaningful guidance at both the U.S. and international levels may help to explain the heterogeneity of offers of payment described in the

[52] Grady, Dickert, Jawetz, Gensler, & Emanuel, *supra* note 16, at 370.

[53] *Id.*

[54] *Id.* See also, Quorum Review IRB, *The Ethics of Compensation for Healthy Trial Participants*, http://www.quorumreview.com/2015/09/10/ethics-compensation-healthy-trial-participants/ (last visited Feb. 16, 2016).

[55] The individuals who experienced severe adverse reactions in the 2006 TeGenero trial were paid approximately $3,500 to participate. Meredith Wadman, *London's Disastrous Drug Trial Has Serious Side Effects for Research*, 440 NATURE 388, 388 (2006).

preceding section, as well as the conservative approaches to payment we see both anecdotally[56] and in many institutional policies, as described in Part V.

A. American Regulations and Guidelines

Federal laws governing human subjects research demonstrate "a societal commitment to the advancement of scientific knowledge provided that the advances occur in accord with ethically sound principles and practices."[57] Although federal regulations and guidelines call attention to some of the ethical issues that payment raises, they offer little substantive guidance regarding how ethically to offer payments to research participants.[58]

1. The Belmont Report

The BELMONT REPORT,[59] promulgated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is one of the foundational documents of bioethics, setting forth ethical principles and guidelines to govern the

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[56] *See, e.g.*, Eleanor Singer & Robert Bossarte, *Incentives for Survey Participation: When Are They Coercive?*, 31 AM. J. PREV. MED. 411, 413 (2006) (relating how IRBs have "increasingly said" that $40 to $100 incentives for survey response have been deemed "coercive").

[57] Jonathan Moreno, Arthur L. Caplan, Paul Root Wolpe, & Members of the Project on Informed Consent, Human Research Ethics Group, *Updating Protections for Human Subjects Involved in Research*, 280 JAMA 1951, 1951 (1998).

[58] Dickert & Grady, *supra* note 34, at 199.

[59] NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH (NAT'L COMM'N), ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979). Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission") in 1974 amidst "public outrage and congressional uncertainty over the Tuskegee syphilis experiments and other questionable uses of humans in research." Tom L. Beauchamp, *The Belmont Report*, 149 in THE OXFORD TEXTBOOK OF RESEARCH ETHICS, (Eds. Ezekiel J. Emanuel, Christine C. Grady, Robert A. Crouch, Reider K. Lie, Franklin G. Miller, and David D. Wendler).

conduct of human subjects research. The report itself is not legally binding, but we begin with it here because its principles underlie the current U.S. federal regulations.[60]

The BELMONT REPORT explains that "[r]espect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied."[61] As described above, informed consent is understood to ensure that individuals control whether they participate in research and that they participate only when participation is consistent with their values, preferences, and interests. The BELMONT REPORT states that

> [a]n agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. **Coercion** occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. **Undue influence**, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influence if the subject is especially vulnerable.[62]

The authors of the BELMONT REPORT clearly understood coercion and undue inducement to be two distinct concepts, but it is implied that both affect the voluntariness of consent. It is worth noting that they resisted drawing a bright line between that which is

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[60] David A. Hyman, *Institutional Review Boards: Is this the Least Worse We Can Do?*, 101 NW U. L. REV. 749, 750 n.3 (2007) ("Although there were classified regulations governing human experimentation issued by the Atomic Energy Commission and Department of Energy in the 1940s and 1950s, and the National Institutes of Health issued regulations on research involving human subjects in 1966, most scholars date the beginning of comprehensive feral regulation of human subjects research to 1974, when the regulation that ultimately gave rise to the Common Rule was issued.").

[61] NAT'L COMM'N, *supra* note 59, at n.p.

[62] *Id*. (emphasis added).

a mere inducement (i.e., ethically acceptable) and that which is *undue* (i.e., ethically unacceptable), instead emphasizing the contextual nature of undue inducements. The BELMONT REPORT does not directly address payment.

2. The Common Rule

The Federal Policy for the Protection of Human Subjects is codified in the separate, but identical, regulations of eighteen Federal departments and agencies, and accordingly referred to as the "Common Rule."[63] The Common Rule is "a uniform regulatory floor for human subjects research . . . which generally requires informed consent, independent ethical review, and the minimization of avoidable risks."[64] Common Rule standards apply to all research funded by these eighteen departments and agencies, regardless of where that research occurs. The FDA has not adopted the Common Rule, but applies essentially the same standards to all clinical investigations of products regulated by FDA involving human subjects, regardless of funding source.[65]

The Common Rule requires IRBs to ensure that investigators will secure research participants' informed consent.[66] It states that "[a]n investigator shall seek [informed] consent only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of

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[63] PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES (PCSBI), MORAL SCIENCE: PROTECTING PARTICIPANTS IN HUMAN SUBJECTS RESEARCH, at 2 (2011), http://bioethics.gov/sites/default/files/Moral%20Science%20June%202012.pdf. All participating departments and agencies include language identical to that of the HHS codification at 45 CFR 46, subpart A in their chapters of the Code of Federal Regulations (CFR). We will, therefore, refer to the HHS regulations.

[64] *Id.*

[65] 21 CFR 50, 56.

[66] 45 CFR § 46.116 (2005).

coercion or **undue influence**."[67] The Common Rule does not define either term, nor does it directly address offers of payment. However, to the extent such offers trigger concerns about either coercion or undue influence, they fall within the IRB's regulatory purview to address and responsibility to resolve.

The fact that the Common Rule (and its FDA equivalent) cover almost all clinical research conducted in the U.S., and a broad swath of research conducted abroad,[68] underscores the important role of IRBs in reviewing offers of payment to research participants and understanding the many open questions IRB members—and investigators—face when assessing the acceptability of said offers.

3. OHRP Frequently Asked Questions About Human Research

Created in 2000,[69] OHRP is the office within HHS that "provides clarification and guidance, develops educational programs and materials, maintains regulatory oversight, and provides advice on ethical and regulatory issues in biomedical and behavioral research"[70] funded or conducted by the Department. OHRP's website addresses a number of Frequently Asked Questions (FAQs) about human subjects research, including questions regarding offers of payment. Because the FAQs "provide guidance that represents OHRP's

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[67] 45 CFR 46.116 (2009) (emphasis added).

[68] PCSBI, *supra* note 63, at 31, 39–40.

[69] Before OHRP was formed, the Office for Protection from Research Risks (OPRR) was housed at the NIH. OPRR was dissolved in 2000 and responsibility was transferred to the office of the Secretary of Health and Human Services.

[70] HHS, *About OHRP*, http://www.hhs.gov/ohrp/about/; *see also* Scott Burris & Jen Welsh, *Regulatory Paradox: A Review of Enforcement Letters Issued by the Office for Human Research Protection*, 101 Nw. U. L. Rev. 643, 647 (2007).

current thinking on these topics",[71] they offer helpful insight, though they "should [merely] be viewed as recommendations, unless specific regulatory requirements are cited."[72]

On the one hand, OHRP acknowledges that "[p]aying research subjects in exchange for their participation is a common and, in general, acceptable practice."[73] On the other, it cautions that despite, or perhaps because of, the "lack of clear-cut standards on the boundaries of inappropriate and appropriate forms of influence, investigators and IRBs *must be vigilant* about minimizing the possibility for **coercion** and **undue influence**."[74] One might infer that a call to be "vigilant" from an important oversight body—one with a variety of enforcement mechanisms available to it, including institution-wide suspension of research—coupled with limited substantive guidance on how best to offer payment to research participants could lead to extreme caution and support expansive understandings of coercion and undue inducement. Although a review of OHRP enforcement letters in complaint-initiated investigations uncovered only a handful of instances in which the agency found "unethical inducement through large offers of money,"[75] the mere threat of regulatory action in this space is often enough to shape behavior.[76]

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[71] OHRP, *Frequently Asked Questions about Human Research*, http://www.hhs.gov/ohrp/policy/faq/.

[72] *Id.*

[73] OHRP, *When Does Compensating Subjects Undermine Informed Consent or Parental Permission?*, http://www.hhs.gov/ohrp/policy/faq/informed-consent/when-does-compensating-subjects-undermine-informed-consent.html.

[74] *Id.* (emphasis added).

[75] Burris & Welsh, *supra* note 70, at 664.

[76] Consider, for example, that FDA inspection activity has a deterrent effect on industry non-compliance, though only a small portion of clinical trial sites are inspected. Mary K. Olson, *Agency Rulemaking, Political Influence, Regulation, and Industry Compliance*, 15 JLEO 573, 599 (1999). HHS OIG, CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS, http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf (last visited Feb. 14, 2016) (FDA inspected only 1.9% of domestic clinical trial sites).

a. Definitions

In one FAQ, the following question is posed: "What does it mean to minimize the possibility of coercion or undue influence?"[77] In response, OHRP provides definitions of coercion and undue inducement that largely—though incompletely—align with those found in the BELMONT REPORT, as well as examples.

> **Coercion** occurs when an overt or implicit threat of harm is intentionally presented by one person to another in order to obtain compliance. For example, an investigator might tell a prospective subject that he or she will lose access to needed health services if he or she does not participate in the research.[78]
>
> **Undue influence**, by contrast, often occurs through an offer of an excessive or inappropriate reward or other overture in order to obtain compliance. For example, an investigator might promise psychology students extra credit if they participate in the research. If that is the only way a student can earn extra credit, then the investigator is unduly influencing possible subjects. If, however, she offers comparable non-research alternatives for earning extra credit, the possibility of undue influence is minimized.[79]

With respect to undue inducement, the FAQ observes that "it is often difficult for IRBs to draw a bright line delimiting undue influence" because it is highly contextual.[80]

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[77] OHRP, *What does it mean to minimize the possibility of coercion or undue influence?*, http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-does-coercion-or-undue-influence-mean.html.

[78] Elsewhere within the FAQs, "**overt coercion**" is defined as "e.g., threatening loss of services or access to programs to which the potential subjects are otherwise entitled." OHRP, *Can non-financial enrollment incentives constitute undue influence?*, http://www.hhs.gov/ohrp/policy/faq/informed-consent/can-non-financial-enrollment-incentives-constitute-undue-influence.html (emphasis added).

[79] *Id.*

[80] *Id*.

b. Substantive Recommendations Regarding Payment

OHRP acknowledges that "difficult questions must be addressed by the IRB."[81] The FAQ "When does compensating subjects undermine informed consent or parental permission?" advises that:

- "Remuneration for participation in research should be just and fair. However, the specifics of each protocol will influence how those determinations are made. Both researchers and IRBs need to be familiar with the study population and the context of the research in order to make reasonable judgments about how compensation might affect participation."[82]
- "IRBs should be cautious that payments are not so high that they create an '**undue influence**' or offer **undue inducement** that could compromise a prospective subject's examination and evaluation of the risks or affect the voluntariness of his or her choices."[83]
- "IRBs and investigators should ensure that the consent process includes a detailed account of the terms of payment, including a description of the conditions under which a subject would receive partial or no payment (e.g., what will happen if he or

[81] *Id.*

[82] OHRP, When does compensating subjects undermine informed consent or parental permission?, http://www.hhs.gov/ohrp/policy/faq/informed-consent/when-does-compensating-subjects-undermine-informed-consent.html# (last visited Jan. 12. 2016).

[83] *Id*. (emphasis added).

she withdraws part way through the research or the investigator removes a subject from the study for medical or noncompliance reasons)."[84]

- "[I]n studies of considerable duration or that involve multiple interactions or interventions, OHRP recommends that payment be prorated for the time of participation in the study rather than delayed until study completion, because the later could **unduly influence** a subject's decision to exercise his or her right to withdraw at any time."[85]

It noteworthy that this FAQ links offers of payment *only* to undue inducement and not to coercion. It does not, however, explicitly say that offers of payment cannot be coercive. Additionally, it suggests that undue inducement affects the voluntariness element of consent.

In a note accompanying this FAQ, OHRP asserts that "IRBs should not consider remuneration as a way of offsetting risks" when deciding whether or not to approve research, but recognizes that "remuneration to subjects may include compensation for risks associated with their participation in research and that compensation may be an acceptable motive for agreeing to participate in research."[86]

[84] *Id.*

[85] *Id.* (emphasis added).

[86] *Id.*

4. FDA Information Sheet

The FDA also offers an Information Sheet on Payment to Research Subjects,[87] which like the OHRP FAQs is a non-binding guidance document, but also the most extensive guidance IRBs have when seeking to implement and adhere to the FDA regulations. The Information Sheet acknowledges that "[i]t is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development."[88]

Among other things, the Information Sheet advises IRBs to "review both the amount of payment and the proposed method and timing of disbursement to assure that neither are **coercive** or present **undue influence**."[89] Specific guidelines for evaluating offers of payment include:

- "All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document."[90]
- "Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a **coercive** practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed

[87] FDA, *Payment to Research Subjects—Information Sheet*, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm (last visited Feb. 3, 2016).

[88] *Id*.

[89] *Id.* (emphasis added).

[90] *Id.*

a phase of the study) had they not withdrawn."[91]

- "While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not **coercive**."[92]
- "The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to **unduly induce** subjects to stay in the study when they would otherwise have withdrawn."[93]

Unlike the OHRP FAQ, the FDA guidance clearly links offers of payment to *both* coercion and undue inducement.

B. International Guidelines

While the Common Rule and its FDA equivalent cover most clinical research conducted in the United States,[94] investigators' and IRBs' deliberations regarding what constitutes an acceptable offer of payment may also be influenced by a number of prominent ethical guidelines relating to the conduct of biomedical research. Some countries have adopted these as regulatory requirements, while in other places, they are merely advisory. Investigators may voluntarily import them into protocols or be mandated to do so under certain conditions.

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[91] *Id.* (emphasis added).

[92] *Id.* (emphasis added).

[93] *Id.* (emphasis added).

[94] PCSBI, *supra* note 63, at 31, 39–40.

Many of these international guidelines were written in the aftermath of ethics scandals or in response to the perceived shortcomings of prior documents.[95] As a result, there is a tendency to emphasize some ethical requirements while overlooking others.[96] This context may help explain why the guidelines provide little specific guidance regarding offers of payment.

1. Nuremburg Code

The Nuremberg Code was formulated by American judges "sitting in judgment of Nazi doctors accused of conducting murderous and torturous human experiments in the concentration camps."[97] Although the Code says nothing about payment specifically, it does address coercion. The first principle is: "The voluntary consent of the human subject is absolutely essential." The Code goes on to specify that "[t]his means that the person involved should . . . be able to exercise free power of choice, without the intervention of any element of . . . **coercion**; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision."[98] Coercion is not defined, however.

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[95] Emanuel, Wendler, & Grady, *supra* note 21, at 2701.

[96] *Id*. at 2701–2702 (offering examples of selective emphases and oversights).

[97] Evelyne Shuster, *Fifty Years Later: The Significance of the Nuremberg Code*, 337 NEJM 1436, 1436 (1997).

[98] "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council of Law No. 10," Vol. 2, pp. 181-182. Washington, DC: U.S. Government Printing Office, 1949 (emphasis added).

2. Declaration of Helsinki

The World Medical Association's Declaration of Helsinki is "a statement of ethical principles for medical research involving human subjects . . . . addressed primarily to physicians."[99] Like other guidelines and regulations discussed in this article, the Declaration places an emphasis on the importance of voluntary consent to participation in research. Additionally, the 2013 revision of Declaration states that "[t]he protocol should include information regarding . . . incentives for subjects" and be submitted for consideration and approval to an IRB.[100] The Declaration does not define coercion or undue inducement, nor does it raise these concerns in relation to offers of payment.[101]

3. Good Clinical Practice Guidelines

The International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines are "an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects."[102] They provide "a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions."[103]

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[99] WMA, *supra* note 20, at n.p.

[100] *Id.*

[101] *Id.* (stating only that the research ethics committee must be free of "any other undue influence").

[102] HHS, Guidance for Industry E6 Good Clinical Practice: consolidated Guidance, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf.

[103] FDA, *ICH Guidance Documents*, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm (last visited Feb. 12, 2016).

According to the ICH GCP E6 guidelines, the IRB should "review both the amount and method of payment to subjects to assure that neither presents problems of **coercion** or **undue influence** on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject."[104] Additionally, the IRB "should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified."[105] Unlike the OHRP FAQs but like the FDA information sheet on payment, the GCP guidelines suggest that payments can be both coercive and unduly influential. Neither term is defined.

4. CIOMS International Ethical Guidelines for Biomedical Research

Compared with the preceding guidelines, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), offer a more definitive answer to questions about offers of payment to research participants.[106] Guideline 7 (Inducement to Participate in Research) states:

> Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better

[104] Guidance for Industry E6, *supra* note 102, at 11 (emphasis added).

[105] *Id.*

[106] CIOMS, *supra* note 20, at n.p (emphasis added).

> judgment ("**undue inducement**"). All payments, reimbursements, and medical services provided to research subjects must have been approved by an ethical review committee.

The Commentary on Guideline 7 explains further:

> Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and **undue influence** to participate in research. . . . Monetary and in-kind recompense must, therefore, be evaluated in light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute **undue influence**. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances.[107]

While CIOMS offers the most explicit guidance regarding offers of payment to research participants, it still leaves a considerable amount of discretion to the IRB to determine what constitutes an acceptable offer of payment. Emphasis is placed on the possibility that offers of payment will be unduly influential, rather than coercive.

In 2015, updates were proposed to the CIOMS Guidelines.[108] One notable change is the strong stance adopted toward offers of payment. Whereas the 2002 (and still current) CIOMS Guidelines state research participants "*may* be reimbursed,"[109] Proposed Guideline 13 asserts that participants "*must* be reasonably reimbursed for direct and indirect expenses incurred during the research, such as travel costs and lost earnings, and compensated reasonably for inconvenience and time spent."[110] The accompanying

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[107] *Id.* (emphasis added).

[108] *See generally,* Emily A. Largent, *Recently Proposed Changes to Legal and Ethical Guidelines Governing Human Subjects Research*, J. L. BIOSCIENCES (2016), doi:10.1093/jlb/lsw001.

[109] CIOMS, *supra* note 20, at n.p.

[110] CIOMS, REVISION OF CIOMS 2002 INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS: DRAFT GUIDELINES (2015), available at

commentary asserts that "[p]articipants should not have to pay for making a contribution to the social good of research."[111] Beyond mere reimbursement, the commentary points out that "[e]specially when the research poses low risks, providing compensation for participating usually does not raise concerns about **undue inducement**."[112] Although not yet final, this is notable among all the guidance discussed so far, as it is the only statement of a reason *not* to worry about payment in some contexts.

III. An Argument Against Research Exceptionalism With Regard to Payment

As Part II established, regulations and guidelines regarding offers of payment to research participants generally establish as the default that such offers are to be subjected to scrutiny because they may be unduly influential, coercive, or both, and so might undermine the validity of research participants' informed consent. Given this default, it is perhaps unsurprising that in the context of human subjects research, offers of payment are often viewed with a high index of suspicion, despite being quite common. We attribute much of the concern about offers of payment to research participants to the problem of research exceptionalism.

Many people have been taught—or intuitively believe—that research is meaningfully different than other areas of life in which we accept burdens, discomforts, and risks. They are, therefore, much more concerned about threats to the validity of consent posed by payment in the research context than they are in other contexts, such as

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http://www.cioms.ch/images/stories/guidelines_demo/AllGuidelines-1-25.pdf (last visited Jan. 4, 2015) (emphasis added).

[111] *Id.*

[112] *Id.* (emphasis added).

employment.[113] As a result, research in general, and offers of payment made to research participants in particular, are more stringently regulated and scrutinized than many other activities that involve both payment and the imposition of seemingly similar—or even greater—levels of risk.[114] While people often worry that offers of payment made to research participants may be too high, we do not hear comparable concerns voiced about payment to individuals engaged in risky work, such as police offers, firefighters, pilots, and even commercial truck drivers.[115] Indeed, many would argue that these individuals are not paid enough. Why the disparity?

Of course, the fact of this disparity is not in and of itself proof that the current level of oversight and scrutiny applied to clinical research payments is, as a normative matter, too great. Instead, one might argue that (1) offers of payment made *elsewhere* are insufficiently scrutinized, and that we should not level-down in the research context, or (2) there are sound ethical reasons why offers of payment made to research participants in particular should be treated differently.[116] Position (2) is consistent with a view of justified research exceptionalism.

Here, we will identify nine arguments made in favor of research exceptionalism and show that they ultimately fail to justify the more stringent regulation of offers of payment made to research participants. There may, we concede, be reasons to think that research is meaningfully different from other contexts and that some enhanced protections are

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[113] Largent, Grady, Miller, & Wertheimer, *supra* note 24, at 507.

[114] James Wilson & David Hunter, *Research Exceptionalism*, 10 AM. J. BIOETHICS 45, 45 (2010) (offering a "qualified defense" of research exceptionalism).

[115] It may be that people in these jobs deserve higher payments for a variety of reasons—such as shift-work and specialized training—but risk is among them.

[116] *Cf. id.*

appropriate for research participants. However, in our view, these reasons do not relate to payment.

A. History of Ethical Abuses

Probably the foremost reason given in favor of special regulation of human subjects research is the history of egregious ethical abuses.[117] Many of the ethical guidelines and regulations governing human subjects research have grown out of particular scandals.[118] Thus, there is a prominent cycle of scandal-and-reform that has led to a progressive ratcheting up of research participant protections.[119] While we don't dispute the seamy history, we agree with James Wilson and David Hunter that:

> These cases do provide prima facie evidence that unregulated research can be abused. However, they fall short of demonstrating the case for research exceptionalism. . . . First, they do not show that these risks are specific to research: Abuses can and have occurred in many other areas of human existence. Second, they do not show that regulation will prevent these abuses. To justify research exceptionalism, we need to demonstrate that there are risks that are *either specific to research or are more likely in research*.[120]

Additionally, and most importantly for our purposes, these foundational and transformational abuses have nothing directly to do with offers of payment. Instead, they

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[117] *See generally*, Henry K. Beecher, *Ethics and Clinical Research*, 274 NEJM 1354 (1966) (detailing examples of unethical and questionably ethical studies).

[118] Emanuel, Wendler, & Grady, *supra* note 21, at 2701.

[119] Other ethics regulations also file follow this scandal-reform dynamic. *See, e.g.,* G. CALVIN MACKENZIE, SCANDAL PROOF: DO ETHICS LAWS MAKE GOVERNMENT ETHICAL? (2002) (discussing cumulative efforts to regulate the ethical behavior of executive branch officials).

[120] Wilson & Hunter, *supra* note 114, 49 (2010) (emphasis added).

were related to concerns with outright torture (e.g., Nazi experimentation[121]), deception (e.g., the Tuskegee syphilis studies[122]), researcher conflicts of interest (e.g., the Jesse Gelsinger gene therapy case[123]), and the like.

Even in high-profile cases where the offer of payment was subsequently subject to scrutiny, ethical fault laid with the way the trials were conducted, rather than with the offer of payment itself (e.g., the TeGenero TGN1412 trial[124]). Critically, the tragic outcomes attributable to ethical violations in these cases would have been no more acceptable if payment had *not* been offered to research participants.[125] The mere fact that money was offered to research participants should not, therefore, bias our evaluation of whether research was conducted ethically. Scandal does not make payment in the research context exceptional.

B. Risk of Harm to Research Participants

Another common argument given in support of research exceptionalism is that research exposes participants to risk of harm. Research-related risks can be analyzed as a

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[121] George J. Annas & Michael A. Grodin, *The Nuremberg Code*, 136 at 136–137 in THE OXFORD TEXTBOOK OF RESEARCH ETHICS, (Eds. Ezekiel J. Emanuel, Christine C. Grady, Robert A. Crouch, Reider K. Lie, Franklin G. Miller, and David D. Wendler) ("The victims who did not die in the course of such experiments surely wished that they had.").

[122] *See generally*, JAMES H. JONES, BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT (1992).

[123] Gelsinger, who was 18 years old, participated in a gene therapy trial at the University of Pennsylvania. He experienced a severe immune reaction to the vector (i.e., the gene's delivery vehicle) and became the first person to die because of participation in gene-therapy research. The major questions after his death involved informed consent and conflict of interest disclosure. Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, THE NY TIMES MAGAZINE (Nov. 28, 1999).

[124] *See generally,* Ezekiel J. Emanuel & Franklin G. Miller, *Money and Distorted Ethical Judgments about Research: Ethical Assessment of the TeGenero TGN1412 Trial*, 7 AM. J. BIOETHICS 76 (2007). *See also*, Wadman, *supra* note 55.

[125] *Id.* at 78.

function of two distinct components: (1) the likelihood that harm will occur, and (2) should it occur, the magnitude of the harm.[126] Because clinical research involves interventions about which knowledge is limited, "research inherently entails uncertainty about the degree of risk . . . with earlier phase research having greater uncertainty."[127]

Admittedly, participation in research can be associated with significant risks: individuals have been seriously injured and even died as a result of their participation.[128] Yet, "research participation . . . is not usually as risky as the general public perceives it to be."[129] Additionally, many quotidian activities expose individuals to at least some risk of harm. The pervasive nature of risk is acknowledged in the Common Rule, which defines minimal risk research in terms of risks "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[130] Even granting that some research studies are particularly risky, "[i]t is not clear that research per se is specifically risky,"[131] as compared to things like police work, military service, and the like. While some risks that people encounter in their lives are regulated, others are not. Therefore, the risk of harm does not itself justify research exceptionalism.

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[126] Annette Rid, Ezekiel J. Emanuel, & David Wendler, *Evaluating the Risks of Clinical Research*, 304 JAMA 1472, 1473 (2010).

[127] Emanuel, Wendler, & Grady, *supra* note 21, at 2705.

[128] *See, e.g.*, Julian Savulescu, *Harm, Ethics Committees, and The Gene Therapy Death*, 27 J. Med. Ethics 148 (2001) (discussing the death Jesse Gelsinger); Robert Steinbrook, *Protecting Research Subjects—The Crisis at Johns Hopkins*, 346 NEJM 716 (2002) (discussing the death of 24-year-old Ellen Roche in an asthma study).

[129] Lynch, *supra* note 42, at 133. *See generally*, Chris J.D. Zarafonetis, Philip A. Riley, Park W. Willis, Lawrence H. Power, et al, *Clinically Significant Adverse Effects in a Phase 1 Testing Program*, 24 Clinical Pharmacology & Therapeutics 127 (1978).

[130] 45 CFR 46.102.

[131] Wilson & Hunter, *supra* note 114, at 49.

The argument from risk of harm also clearly fails when applied more narrowly to offers of payment to research participants.

> [I]n theory, the market should dictate (and some laws do) that risky work be better compensated, a phenomenon called the compensating wage differential. Further, even when risky jobs are held by those with few other options for less risky work that is comparably compensated, the law does not require that their payment be restricted on that basis.[132]

There is little normative debate about whether it is acceptable to offer payment, or higher payment, to people who accept risky jobs. To the contrary, outside the research context, the main concern seems to be that people will be unfairly compensated—that is, exploited—if they are paid too *little*. For example, "[t]he life-and-death nature of the job [policing] is used to push for extremely generous . . . pay packages."[133] Thus, the fact that research participation exposes people to risk of harm cannot stand alone as an argument against offering payment—even generous payment—research participants.

C. Uncertainty of Risk in Research

The next possibility we consider is that it is not the risk of harm per se but some characteristic of that risk that justifies research exceptionalism. For example, it might be that the risk in research is uniquely amorphous. Research is, after all, intended to answer open questions, and "[u]ncertainty is a fundamental characteristic of research."[134]

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[132] Lynch, *supra* note 42, at 157 (internal citations omitted).

[133] David Feige, *The Myth of the Hero Cop*, http://www.slate.com/articles/news_and_politics/politics/2015/05/the_myth_of_the_hero_cop_police_unions_have_spread_a_dangerous_message_about.html (last visited Jan. 14, 2016).

[134] Wilson & Hunter, *supra* note 114, at 51.

Therefore, at the outset, it may be impossible to know with certainty the scope of potential or likely harms—as well as the potential benefits—faced by research participants.[135]

Yet, there is less uncertainty about research risks than it may appear, particularly as investigational products proceed through their development. Before a study of a new FDA-regulated product can proceed to human trials, for example, FDA must be convinced that there is adequate data from laboratory and animal testing to support the claim that the drug is safe enough to give to research participants;[136] IRB approval will be required as well, as a further check on whether the risks are appropriately minimized and reasonable. Moreover, as clinical research progresses through the different phases, there will be a substantial accretion of data; therefore, uncertainty should dissipate over time.

While granting that there is some degree of uncertainty in clinical research, it is necessary to point out that there is uncertainty about risks in many contexts—consider, for example, exposure to environmental pollutants, or even approved drug products. When risk is uncertain, regulation can be an appropriate response, but the key observation to our present analysis is that it is not clear why research should be regulated *more* stringently than other areas similarly characterized by uncertainty.

Looking to offers of payment specifically, even if uncertainty about research risks was somehow unique, it is unclear why that uncertainty would be a reason to pay research participants *less*. Above, we discussed the compensating wage differential for risky work, and here, we would reiterate that it may be appropriate to pay research participants *more*

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[135] *Id.*

[136] *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last visited Jan. 7, 2016). *See also IND Application Procedures: Clinical Hold*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362971.htm (last visited Feb. 18, 2016).

when risks are uncertain, precisely as compensation for that uncertainty. The argument from uncertainty of risks does not necessarily or even obviously lead to the conclusion that offers of payment to research participants should be constrained, and so further justificatory work is needed to defend research exceptionalism with respect to payment.

D. Risk Assumed for the Benefit of Others

A fourth possible argument in favor of research exceptionalism is that the purpose of research is to generate socially valuable knowledge. Research-related risks and burdens are justified not in light of the potential to benefit the individual research participant but in light of their potential to benefit future patients. In research, unlike in other activities, the argument goes, there is tension between the individual good and the public good because risk is assumed for the benefit of others, and so additional scrutiny is needed.

This apparent distinction also proves illusory, however. First, at least some individuals may in fact benefit from participation in research, for example from a successful experimental intervention or from free medical care that is delivered in the course of the study.[137] Even when individuals are motivated to participate in clinical research solely by altruism, they may benefit by contributing to research when they share the ends for which the research is undertaken.[138]

Second, assumption of risk in other areas of life cannot accurately be characterized as entirely self-interested; it is often also for the benefit of society. Again, consider the

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[137] King, *supra* note 31, at 333. While payments made to research participants are, technically, a collateral benefit, they are treated separately in research ethics and policy. *Id.*

[138] *Cf.* Lynn A. Jansen, *The Problem with Optimism in Clinical Trials*, 28 IRB: ETHICS & HUMAN RESEARCH 13, 18 (2006).

police officer or commercial fisherman. While it is clearly in their personal interests to work in order to collect a paycheck, those jobs only exist because *others* incur a benefit from their existence and, therefore, create demand for people to do those jobs. Even in the case of commercial fishing, where the social benefit is merely satisfying consumers' taste for fish, society allows fishermen to take risks at least in part for the benefit of others and to be compensated for it.

We would argue that if society is willing to pay people to engage in risky but socially beneficial activities (even when the benefits are arguably frivolous), "then consistency seems to require that they also be allowed to receive payments for participating in socially beneficial research involving serious risk."[139] Thus, the argument that risk is assumed for the benefit of others in clinical research also fails to support the exceptional scrutiny given to research payments.

E. The Optional Nature of Medical Progress

A fifth possible argument—a variant of that just considered—is that medical progress is optional, whereas other risky but socially beneficial endeavors are not. Hans Jonas has, for instance, admonished us "not [to] forget that progress [in the conquest of disease] is an optional goal."[140]

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[139] Terrence F. Ackerman, *An Ethical Framework for the Practice of Paying Research Subjects*, 11 IRB: ETHICS AND HUMAN RESEARCH 1, 1 (1989).

[140] Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, DAEDALUS 219, 245 (1969). Jonas goes on to say, "Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having." *Id.*

Arguing specifically against payment of research participants, Paul McNeil concedes that some dangerous work, such as firefighting, is necessary, but he denies that "experiments are . . . necessary to society in the way in which some dangerous work may be."[141] He argues that the risks of research cannot be justified in the same way as the risks of necessary work. McNeil's distinction, fails, however.

> If dangerous work such as fire fighting is necessary . . . why is dangerous work such as research participation — which may also save lives and meet basic human needs — any less so? There seems to be no reason to distinguish between different types of potentially preventable deaths when people have voluntarily put themselves at risk in the service of a greater good.[142]

On our view, medical progress is not optional. Some kinds of research are morally obligatory to conduct, assuming they can be conducted ethically. One might respond that a fire fighter who rushes into a burning building to save someone offers an *immediate* benefit, whereas participation in research results in saved lives over a much longer time-scale. Admittedly, that will often be the case. Yet, as a matter of intergenerational equity, it is unclear why we should favor lives currently in existence (or presently in jeopardy) over lives not yet in existence (or not presently at jeopardy). Our moral impulse to save identifiable lives should not blind us to the imperative to save statistical lives when possible.[143]

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[141] Paul McNeill, *Paying People to Participate in Research: Why Not?*, 11 BIOETHICS 390, 392 (1997).

[142] Lynch, *supra* note 42, at 157.

[143] In our personal morality, we believe that we do have greater obligations to identified individuals than to individuals unknown to us. Personal morality cannot, however, be neatly transposed on the public sphere. *Cf.* Emily A. Largent & Steven D. Pearson, *Which Orphans Will Find a Home? The Rule of Rescue in Resource Allocation for Rare Diseases*, 42 HASTINGS CENTER REPORT 27, 30 (2012).

Yet, even if we were to assume *arguendo* that medical progress is optional, one must allow that some risky jobs that yield social benefits but are indisputably optional, like commercial fishing, exist without controversy. If we allow payment for those jobs—and we do—then the optional nature of social benefit, if true, could not justify research exceptionalism with respect to payment.

F. Difficulty Securing Research Participants' Informed Consent

Another argument for research exceptionalism stems from the now substantial evidence that many who participate in research suffer from the therapeutic misconception—that is, they confuse the goals of clinical research (social benefit) with the goals of clinical care (individual benefit)—and, at least some individuals may be unaware that they are participating in research at all.[144] More generally, some people may assume the risks of research participation despite failure to fully comprehend them. Some commentators use this fact to argue that "we should not allow people to make significant life choices without fully understanding the potential consequences for their lives."[145]

Yet, as Wilson and Hunter astutely point out, "[W]hile research protocols may be difficult to understand, they are no more difficult and often considerably less difficult to understand than many official documents such as the fine print on mortgage

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[144] *See, e.g.*, Paul S. Appelbaum, Charles W. Lidz, & Thomas Grisso, *Therapeutic Misconception in Clinical Research: Frequency and Risk Factors*, 26 IRB: ETHICS AND HUMAN RESEARCH 1, 4–5 (2004) ("A total of 61.8% (n=139) of participants were judged to have a TM."); Charles W. Lidz, Paul S. Appelbaum, Thomas Grisso, & Michelle Renaud, *Therapeutic Misconception and the Appreciation of Risks in Clinical Trials*, 58 SOCIAL SCIENCE & MEDICINE 1689, 1693 (2004) ("23.9% (n = 37) of subjects reported *no risks or disadvantages* of any sort from participating in these trials."); Steven Joffe, E. Francis Cook, Paul D. Cleary, Jeffrey W. Clark, & Jane C. Weeks, *Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey*, 358 LANCET 1772, 1774 (2001) ("A quarter of respondents did not agree that the main purpose of clinical trials is to benefit future patients. Many did not realise that the treatment being research was not proven to be the best for their cancer.").

[145] Wilson & Hunter, *supra* note 114, at 50.

documentation."[146] The conduct of research—like mortgages—is heavily regulated, and there are calls to make informational documents easier to understand in both contexts.[147] Nevertheless, the fact that it is difficult to secure truly informed consent from research participants does not, on its own, justify research exceptionalism. True understanding is a challenge in many contexts.

In fact, difficulty in securing research participants' genuinely informed consent may be a stronger argument *in favor of* payment than against it. Offers of payment may help research participants distinguish clinical research from clinical care, since offering payment to research participants "might send the message that they were participating in these trials for the sake of science and should be compensated for it, which would not occur if they were . . . expected to benefit from it."[148] Certainly, our doctors do not pay us in the course of clinical care; instead, we pay them. Accordingly, any offer of payment might help flag for research participants the distinct risks and burdens of research, presumably with higher payments offering even stronger signals. This is an empirical claim that deserves further examination.

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[146] *Id.*

[147] The Consumer Financial Protection Bureau's (CFPB) Know Before You Owe mortgage disclosure rule is "designed to help consumers . . . avoid costly surprises at the closing table." *Know Before you Owe | Mortgages*, http://www.consumerfinance.gov/know-before-you-owe/ (last visited Jan. 15, 2016). Similarly, the NPRM aims to address concerns that "[i]nformed-consent documents grow ever longer and consistently exceed the eighth-grade reading level, with wide variation in participants' comprehension." Ezekiel J. Emanuel, *Reform of Clinical Research Regulations, Finally*, 373 NEJM 2296, 2297 (2015).

[148] William Glannon, *Phase I Oncology Trials: Why the Therapeutic Misconception Will Not Go Away*, 32 J. MED. ETHICS 252 (2008) ("[T]his option at best would ameliorate but not resolve the problem of misperception about research."). *See also*, Dickert & Grady, *supra* note 34, at 198.

G. Commodification

One potential justification for research exceptionalism with respect to payment in particular is that offering to pay people who participate is wrongful commodification. It has been said, for example, that "[p]ayment to patients to serve as research subjects is an ethically unacceptable commodification of research practice."[149] Individuals concerned with commodification feel that it is improper to offer money for certain goods or services, even if the validity of the consent is not in doubt. This may be a threshold concern as to whether payment can be offered at all—and not just the amount of payment.

Commodification concerns do animate certain laws and policies outside the research context. For example, a central provision of the National Organ Transplant Act (NOTA), § 301(a), bans the buying and selling of human organs.[150] The legislative history of NOTA clearly shows that Congress felt that buying and selling of organs was contrary to society's moral values.[151] One might question—as many have—whether prohibitions against organ sales are appropriate on these grounds.[152] Yet, even if one accepts that commodification concerns are relevant in some contexts, *services* offered by research participants are not the same as selling the constituent *parts* of one's body. As we have suggested throughout this section, participation in research is most appropriately

[149] Ruth Macklin, *The Paradoxical Case of Payment as Benefit to Research Subjects*, 11 IRB: ETHICS AND HUMAN RESEARCH 1, 3 (1989).

[150] 42 U.S.C.A. §274e(a) (2000).

[151] Emily A. Largent, *NOTA: Not A Good Act for Tissues to Follow*, QUINNIPIAC HEALTH LAW JOURNAL, forthcoming (2016) (analyzing prohibitions against the sale of human organs and tissues).

[152] *See id.*

analogized to essential (albeit unskilled) labor.[153] In the context of unskilled labor—and skilled labor as well—we generally permit people to sell their bodily services,[154] even when sale of those services exposes them to risk of bodily harm. It should be "no more worrisome to commodify a person's labor as a research subject than to commodify a person's labor in other contexts, which happens all the time."[155]

H. Crowding Out Altruism

Another argument for research exceptionalism regarding payment is that it is desirable to recruit altruistically motivated individuals to participate in research studies, whereas altruism may not be needed (or as important) in other endeavors. Lynn Jansen observes, "Those who seek to justify clinical research often point to the possibility that participants . . . have altruistic motives for participating."[156] On this argument, offers of payment must be closely scrutinized to avoid the perverse consequence of diluting intrinsic motivation to participate.[157] As mentioned above, a minority of commentators believes that altruism should be the *sole* motivation for research participation.[158] For them, this may be a threshold concern as to whether payment can be offered at all.

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[153] Lynch, *supra* note 42, at 137.

[154] Obvious exceptions would be surrogacy and sex work. While it is beyond the scope of the present article to defend this proposition, we are of the opinion that it should generally be permissible to sell the bodily services of surrogacy and sex. *See, e.g.*, Martha C. Nussbaum, "*Whether From Reason or Prejudice": Taking Money for Bodily Services*, 27 J. LEGAL STUDIES 693 (1998).

[155] Lynch, *supra* note 42, at 159.

[156] Lynn A. Jansen, *The Ethics of Altriuism in Clinical Research,* 39 HASTINGS CENTER REPORT 26, 26 (2009).

[157] *Cf.* RICHARD M. TITMUSS, THE GIFT RELATIONSHIP: FROM HUMAN BLOOD TO SOCIAL POLICY (1997).

[158] Chambers, *supra* note 18, at 48.

Most commentators, however, have focused on the conditions under which offers of payment can be ethical, suggesting that research participation does not have to be exclusively or even primarily altruistic. In practice, research participants—even those who are paid—report a variety of motivations, often including altruism among others.[159] This is comparable to studies of police officers that have found individuals enter the field for both altruistic and practical reasons—including the opportunity to help others and attractive job benefits.[160] This finding is both unsurprising and untroubling; if individuals are capable of satisfying a role's requirements, why should their motivations matter? Moreover, given that a variety of motivations can coexist, there is no clear argument for why altruistic motivation should be valued more highly than financial motivation in research, or than it is (or should be) in other contexts.

Two possible practical implications of crowding out altruistic motivations among research participants in favor of financial motivations are more troubling, and could potentially justify greater scrutiny of offers of payment in the research context than elsewhere. If offering payment dilutes altruistic motivation, this might (1) reduce the overall pool of prospective research participants, i.e., some altruists may not participate at all if payment is offered, and/or (2) selectively appeal to individuals who are somehow less desirable as research participants due to their motivation by payment.[161] While a number of experimental studies have examined the effects of financial incentives on altruistic

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[159] *See generally*, Stunkel & Grady, *supra* note 29.

[160] Anthony J. Raganella & Michael D. White, *Race, Gender, and Motivation for Becoming a Police Officer: Implications for Building a Representative Police Department*, 21 J. CRIMINAL JUSTICE 501, 509 (2004).

[161] *Cf.* Simone A. Glynn, Alan E. Williams, Catherine C. Nass, James Bethel, Debra Kessler, Edward P. Scott, Joy Fridey, Steven H. Kleinman, & George B. Schreiber, *Attitudes Toward Blood Donation Incentives in the United States: Implications for Donor Recruitment*, 43 TRANSFUSION 7 (2003).

motivations in other contexts, particularly blood donation, and generally found results consistent with the crowing out hypothesis,[162] data is needed about research participation in particular. We grant that these concerns may be valid in some research contexts; however, they cannot justify restrictive approaches to payment in *all* instances. Rather, a more tailored approach is appropriate, focused on those situations in which payment might have damaging instrumental effects, and also considering whether those effects might be avoided through mechanisms other than limiting payment.

I. Importance of Public Trust

The final argument we consider in favor of research exceptionalism has nothing to do with protecting research participants themselves, but rather with protecting the research enterprise of which they are a part. Public trust is "essential to secure funding and institutional support for research and to recruit human subjects."[163] Therefore, the argument goes, research exceptionalism is justified if it promotes and preserves the public trust. Wertheimer observed that,

> [w]hereas society accepts with a relative yawn the fact that people incur job related injuries or deaths as coal miners, fishermen, and off-shore oil service workers, society seems to react with great intensity to research related injuries and deaths, as evidenced by the public concern with the Jesse Gelsinger case.[164]

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[162] Nicola Lacetera & Mario Macis, *Do all material incentives for pro-social activities backfire? The response to cash and non-cash incentives for blood donations*, 31 J. OF ECONOMIC PSYCHOLOGY 738, 738 (2010).

[163] David B. Resnik, *Public Trust as a Policy Goal for Research with Human Subjects*, 10 AMERICAN JOURNAL OF BIOETHICS 15, 16 (2010); *see also*, Emily A. Largent, *What's Trust Got to Do with It? Trust and the Importance of the Research-Care Distinction*, 15 AMERICAN JOURNAL OF BIOETHICS 22 (2015).

[164] Wertheimer, *supra* note 41, at 116.

As our replies to prior arguments suggest, we believe the public is mistaken to react more intensely to harms attributable to research participation than to harms attributable to traditional work. Yet, even if that more intense response is mistaken, "the public trust argument maintains that public beliefs are a fact that must be accommodated."[165]

In response, we first note that there is little evidence that "members of the public are both generally aware of the existence of [IRBs] and find the notion reassuring."[166] In other words, they may simply be unaware of the ways in which they are protected from research risks, such that these protections cannot possibly contribute to trust building. More specifically, it is only speculative that research exceptionalism with respect to payment promotes public trust. To the contrary, rigorously restricting offers of payment to research participants—indeed, *protecting* them from offers of payment—could erode public trust by suggesting that research is more dangerous than it really is, and that participation is something to be avoided, even more so than other risky endeavors in which payment is not closely regulated. If individuals nonetheless choose to participate, restricting payment could also cause research participants to feel they have been treated unfairly as a result of inadequate compensation. Beyond these considerations, we believe it would be a mistake to accommodate erroneous beliefs that research is dramatically different from other potentially risky/uncertain endeavors, and instead favor attempts at education that build the right kinds of trust. Therefore, public trust—while doubtlessly important to the research enterprise—is not an acceptable argument for research exceptionalism, particularly with regard to payment.

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[165] *Id.*

[166] Wilson & Hunter, *supra* note 114, at 51.

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We have considered nine arguments sometimes made in favor of research exceptionalism with respect to payment—that is, in favor of the view that offers of payment to research participants need to be regulated more stringently than offers of payment made to individuals in other contexts where they also assume risks for the benefit of others. For the reasons outlined above, we maintain that each of these arguments fails. Significantly, we do not claim that these arguments have failed to identify characteristics of research that might merit regulatory attention; indeed, we favor robust regulatory protections for human subjects research, including IRB review. Rather, we claim that that these nine arguments fail to identify factors that justify regulating offers to payment to research participants more heavily than offers of payment made in other areas.

IV. From Confusion to Clarity: Defining Coercion and Undue Inducement

As we have discussed in the preceding sections, despite a general consensus that coercion and undue inducement are to be avoided, there is a lack of clear regulatory guidance about what constitutes an acceptable offer of payment and disagreement about when offers of payment to research participants violate ethical norms. In this section, we will look at the considerable debate within the research ethics community about how best to define coercion and undue inducement. For both terms, we will highlight areas of consensus, briefly review the range of definitions offered within the literature, and offer our preferred definitions.

A. Coercion

As discussed above, there is a general ethical requirement that prospective participants give their voluntary consent to participate in research.[167] The main worry about coercion is that it affects the voluntariness of consent, and the most prominent definitions from the bioethics literature relate to voluntariness. Here, we will consider three commonly used definitions and also address a divisive question: can offers be coercive?

1. Threatening to Make One Worse Off

Recall that the influential BELMONT REPORT states that coercion "occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance."[168] It is perhaps unsurprising, then, that broad consensus exists that coercion includes the use of a threat of harm to compel another to do something against his or her will.[169] Christine Grady, for example, has stated, "By definition, coercion is understood to involve a threat of physical, psychological, or social harm in order to compel an individual

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[167] Of course, there may be exceptions, such as in emergency research. *See, e.g.*, Emily A. Largent, David Wendler, Ezekiel J. Emanuel, & Franklin G. Miller, *Is Emergency Research without Informed Consent Justified? The Consent Substitute Model*, 170 No. 8 ARCHIVES OF INTERNAL MEDICINE 668 (2010).

[168] NAT'L COMM'N, *supra* note 59, at n.p.

[169] *E.g.*, RUTH FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT, 235-73 (1986); Steven D. Pearson, Franklin G. Miller, & Ezekiel J. Emanuel, *Medicare's Requirement for Research Participation as a Condition of Coverage: Is it Ethical?*, 296 JAMA 988, 989 (2006) ("Coercion occurs when a threat of some harm compels a person to act in a manner that he or she would not otherwise choose. An example is that of a kidnapper demanding ransom. The kidnapped victim's family may be coerced into giving up money to avoid the threatened harm to their loved one.") (internal citations omitted).

to do something, such as participate in research."[170] Given the consistent references to harm, it is generally understood that the person coercing is threatening to make the person coerced *worse off* than he would be at his status quo baseline.

2. Threatening to Violate Rights

Alan Wertheimer[171] and Franklin Miller offer a view of coercion that is similar—but not identical—to that of the BELMONT REPORT.[172] On their rights-violating view of coercion,

> A coerces B to do X in a way that invalidates B's consent only if (1) A proposes or threatens to violate B's rights or not fulfill an obligation to B if B chooses not do X and (2) B has no reasonable alternative but to accept A's proposal. Both conditions are necessary.[173]

Wertheimer and Miller state that "the main point is that A's proposal is coercive only if A's 'declared unilateral plan'—[that is,] what A proposes to do if B does not do X—would violate B's rights."[174] A classic example would be when a mugger pulls a knife on someone and says: "Your money or your life." The mugger is threatening to kill his victim, which would violate the victim's right not to be wantonly harmed by others, if the victim does not acquiesce to surrender his property. Thus, the victim is coerced to hand over his wallet.

Wertheimer and Miller concede that "[t]here is often little difference between the

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[170] Christine Grady, *Payment of Clinical Research Subjects*, 115 J. OF CLINICAL INVESTIGATION 1681, 1683 (2005).

[171] Wertheimer's book COERCION "sets the current standard and starting point for continued scholarship" regarding coercion. Anderson, Scott, "Coercion", *The Stanford Encyclopedia of Philosophy* (Summer 2015 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/sum2015/entries/coercion/>.

[172] Largent, Grady, Miller, & Wertheimer, *supra* note 24, at 505.

[173] Alan Wertheimer & Franklin G. Miller, *Payment for Research Participation: a Coercive Offer?*, 34 J. MED. ETHICS 389, 390 (2008).

[174] *Id.*

worse-off and the rights-violating accounts."[175] After all, both views of coercion will reach the same conclusion in the case of the mugger—what the mugger has done is coercive.

> However, when the two differ, the rights-violating approach is more accurate, because it allows us to handle (1) cases in which A has a right to make B worse off than B's status quo, and also (2) cases in which A has an obligation to render B better off than B's status quo.[176]
>
> To illustrate (1), a prosecutor does not coerce defendants into pleading guilty to a crime in exchange for a relatively lenient sentence when he proposes to take them to trial if they do not plead guilty, even though both options—pleading guilty and going to trial—are worse than B's status quo. Why? Because the prosecutor's declared unilateral plan to take the defendants to trial does not violate their rights relative to *that* option, the prosecutor is actually making an offer of leniency rather than a threat of severity. . . . The defendants' guilty pleas are voluntary.
>
> To illustrate (2), if a physician (A) has an obligation to provide a patient (B) with medical services free of charge, say, because A is employed by the national health service, then A actually does coerce B into paying a fee if A proposes not to provide such services unless B pays. And this is so even though A does not propose to make B worse off than at present if B declines.[177]

We emphasize that in the example for (2), Wertheimer and Miller say A does not propose to make B worse off than B is *at present*. In other words, B is presently untreated, and would continue to be untreated if B refuses to capitulate to A's demand, so B's status quo is unchanged and B is, at least in a sense, not made any worse off. However, A has an obligation to help B achieve something superior to the status quo at present, which is why we find coercion under the rights-violating view when we may not under the worse-off view. Note that there may be disputes about how to identify the appropriate status quo, however, because under an alternative approach, one might suggest that A is indeed

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[175] *Id.*

[176] *Id.*

[177] *Id.*

threatening to make B worse off by failing to achieve the status quo to which B is entitled, which is to be treated by A.

Resolving this question about which status quo baseline is the proper one to focus on under the rights-violating view can be the source of reasonable debate. However, it is unnecessary to resolve the matter here because we argue momentarily that offers of payment cannot be coercive. Thus, in the payment context, it is unnecessary to strictly distinguish between the worse-off and rights-violation definitions of coercion, since neither will be present.

That said, we favor the rights-violating account because of its broader explanatory power. In other words, simply asking if the threat would cause harm inappropriately identifies coercion in scenarios in which harm is justifiable (e.g., when an investigator threatens to remove a subject from a beneficial trial for failure to comply with the study procedures), and might fail to identify coercion when harm is arguably not present, but there is an obligation to make one better off. Importantly, neither the worse-off view nor the rights-violating view of coercion fall prey to research exceptionalism, since they both reflect common views of coercion applied outside of the context of research as well.

3. No Reasonable Alternative

The notion of coercion as existing only when threats of adverse consequences (harm or rights violation) override the exercise of genuinely free choice has been characterized as "cramped" by some commentators.[178] Thus, another proposed definition of coercion is that

[178] Lars Noah, *Coerced Participation in Clinical Trials: Conscripting Human Research Subjects*, 62 ADMIN. L. REV 329, 350 (2010).

an individual is coerced when she has *no reasonable alternative* but to accept another's proposal.[179]

In contrast to the two prior definitions, this definition does not require a threat at all. Proponents of this view classify having no reasonable alternative as a sufficient condition of coercion, not merely a necessary one.[180] Importantly, due to its expansive scope, this approach might result in a substantial portion of research being deemed coercive, since research participation may be a patient volunteer's best available alternative for therapeutic improvement or a healthy volunteer's best available alternative to make a comparable amount of money in a given period of time. Both types of participants may feel that they have no reasonable alternative, even though individuals always have the option not to participate in research as a regulatory matter.

The no reasonable alternative view is clearly wrong if one rejects research exceptionalism. Consider these familiar examples from outside the research context: first, a woman is diagnosed with breast cancer and her oncologist tells her that she is unlikely to survive more than a year without surgery. We would not say that the oncologist has coerced the woman by offering surgery, and it would be nonsensical to claim that the woman cannot give valid consent to the surgical intervention because she has "no choice" but to have it. Second, turning to an instance in which payment changes hands, it is unlikely anyone would say an individual had been coerced to take an unpleasant, risky (but perfectly legal) job if that was his best or even only option to earn sufficient funds to cover his bills. In common parlance, we may suggest that both of these individuals were "forced"

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[179] Joan McGregor, *"Undue Inducement" as Coercive Offers*, 5 AMERICAN J. OF BIOETHICS 24, 25 (2005) (emphasis added).

[180] Wertheimer & Miller, *supra* note 173, at 391.

in some way to make an unpleasant decision, but we would not maintain that there had been any ethical violation. If we do not think that morally problematic coercion occurs in these circumstances, it would be unjustifiable research exceptionalism to argue that it occurs when research participants believe—in the absence of any threat—that they have no reasonable alternative but to participate in research due to an offer of payment.

4. Coercive Offers?

A notable fissure in the literature relates to whether *genuine* offers, rather than threats, can ever be coercive.[181] One of the most visible advocates of the view that offers can be coercive is Ruth Macklin.[182] In a 1989 article, she noted that the "reason for holding that it is ethically inappropriate to pay patients to be research subjects is that [offers of payment are] likely to be coercive."[183] Joan McGregor more explicitly links the concept of coercive offers to the no-reasonable-alternative view just discussed. She explains that coercive offers are "*offers* because they propose to make the person 'better off' relative to his or her baseline . . . but they are *coercive* since, because of the recipient's lack of options, the proposal is likely to present the only eligible choice."[184] Others have accepted that offers may be coercive on the condition that the offerer is responsible for the offeree's bad

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[181] Obviously, a threat may be veiled such that it appears to be an offer (e.g., "I will refrain from shooting you if you give me your money."). This would not be a genuine offer.

[182] Ruth Macklin, *'Due' and 'Undue' Inducements: On Paying Money to Research Subjects*, 3 IRB: ETHICS AND HUMAN RESEARCH 1 (1981). Macklin demurred from saying more about this writing, "Space does not permit a discussion here of the distinction between undue inducement and coercive offers." *Id.* at 3 n.7.

[183] *Id.*

[184] Joan McGregor, *"Undue Inducement" as Coercive Offers*, 5 AMERICAN J. OF BIOETHICS 24, 25 (2005) (arguing that *"undue inducements* might be referred to as 'coercive offers'"); *see also* Joan McGregor, *Bargaining Advantages and Coercion in the Market*, 14 PHILOSOPHY RESEARCH ARCHIVES 23 (1988); Joan L. McGregor, *Free Markets, Bargaining Power, and the Rules of Exchange*, 5 PUBLIC AFFAIRS QUARTERLY 353 (1991).

circumstances.[185]

Many, however, have reached a contrary conclusion and assert that genuine offers (as opposed to veiled threats) cannot be coercive.[186] While threats reduce the choices available to an individual, genuine offers expand the individual's choice set and, therefore, by definition, do not coerce.[187] Wertheimer and Miller are emphatic that the "claim that the offer of financial payments can actually constitute a coercive offer in a manner that undermines informed consent is both false and incoherent, because *genuine offers cannot coerce*."[188] If one thinks that coercion requires a threat (whether of harm or of rights violations), as we do, offers of payment to research participants cannot be coercive.

For emphasis, our view is that *coercion is not a valid or relevant concern when evaluating offers of payment*, although that is not to say that subjects may not be coerced to participate in other ways. This conclusion does not definitively resolve the question of whether offers of payment in the research context are ethically permissible, however, since they may, in some circumstances, cause undue inducement.

B. Undue Inducement

Although there is also a lack of consensus about how to define undue inducement, there are several points of general agreement. First, if an inducement is undue, it could

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[185] Martin Wilkinson & Andrew Moore, *Inducement in Research*, 11 BIOETHICS 373, 378 (1997).

[186] Wertheimer & Miller, *supra* note 173, at 390. *See also*, Alan Wertheimer & Franklin G. Miller, *There are (STILL) no coercive offers*, 40 J. MED. ETHICS 592 (2014); RUTH FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT, 235-73 (1986).

[187] Wertheimer & Miller, *supra* note 173 at 390.

[188] *Id.* at 389.

"prompt subjects to lie, deceive, or conceal information that, if known, would disqualify them as participants in a research project."[189] This not only threatens to harm research participants—for example, by exposing them to risks that the exclusion criteria were designed to shield them from—but also jeopardizes the scientific integrity of the research.

A second area of agreement is that determining the existence of an undue inducement is highly contextual. For example, Emanuel, Wendler, and Grady state, "[L]ocal traditions and economic conditions will influence when financial payments may constitute undue inducements."[190] Wertheimer and Miller suggest that an individual's situation determines whether there is undue inducement; they emphasize that the "distinction between an unproblematic . . . inducement and an undue inducement is not a feature of the inducement itself. It is a function of the relation between the inducement and the subject's response to it."[191] Ruth Grant and Jeremy Sugarman have written that "*[u]nder certain conditions*, incentives are implicated in problems of manipulation in the form of undue influence."[192] Finally, Ruth Macklin explored the question of how large a payment constitutes undue inducement and found it "impossible to arrive at a single, objective

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[189] Macklin, *supra* note 182, at 2. *See also* U.S. DEP'T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK, Chapter 3 (1993) (warning that undue inducements "may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling—or continuing—as participants in a research project"). *But see* Ezekiel Emanuel, *Ending Concerns About Undue Inducement*, 32 J. OF LAW, MED., & ETHICS 100, 103–104 (2004) (stating that it is unclear whether lying is a general problem).

[190] Emanuel, Wendler, & Grady, *supra* note 21, at 2708.

[191] Wertheimer & Miller, *supra* note 173, at 391.

[192] Grant & Sugarman, *supra* note 19, at 732 (emphasis added). For Grant and Sugarman, incentives become problematic when conjoined with "the following factors, singly or in combination with one another. Where the subject is in a dependency relationship with the researcher, where the risks are particularly high, where the research is degrading, where the participant will only consent if the incentive is relatively large because the participant's aversion to the study is strong, and where the aversion is a principled one—when these conditions are present, the use of incentives is highly questionable." *Id.*

criterion serving to mark off due from undue monetary inducements to participate in research."[193]

Taking these areas of consensus as our starting point, we will consider three commonly used definitions of undue inducement and also review the empirical evidence regarding the actual existence of undue inducement in research.

1. Excessive Reward

According to the BELMONT REPORT, "undue influence occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance."[194] On this view, the defining feature of an undue inducement is an offer so disproportionate to what the person is asked to do that it alone appears as evidence of nefarious intent. Of course, what constitutes a disproportionate offer may be subjective.

2. Excessive Reward Producing Bad Judgment Entailing Risk of Harm

Ezekiel Emanuel offers a four-part definition of undue inducements, of which a reward's excessiveness is only one feature:

> First, they entail an offer of a welcomed good, a positive incentive. The induced person is getting something he or she deems desirable. Second, the incentive, by some metric, appears excessive or irresistible. While there is no physical force or external psychological pressure, there is considerable internal attraction because of the quantity or type of the incentive. Third, the incentive does not just make the person do something they are not otherwise induced to do. The incentive must produce bad judgments. Finally, the bad judgments must in turn engender ethically,

[193] Macklin, *supra* note 182, at 2.

[194] NAT'L COMM'N, *supra* note 59, at n.p.

> legally, or prudentially undesirable activities. The activities are undesirable because they contravene the person's interests and thereby harm them. While bad judgment is necessary, alone it is insufficient to constitute undue inducement. Undue inducement requires the action entail a substantial risk of serious harm . . . That is, there must be a risk of a serious adverse effect for the person. Absent potentially serious adverse consequences of the bad judgment there is no undue inducement.[195]

Emanuel stresses that all four elements are necessary for an undue inducement to exist.[196] The first condition, that the thing offered be a positive incentive, immediately distinguishes undue inducement from our preferred view of coercion, which requires a threat. The second condition requires—like the excessive-reward view—that the incentive is large. Condition three distinguishes *undue* inducements from *mere* inducements, which is a critical distinction since mere inducements are not morally problematic (e.g., paying employees a salary so they show up to work, which they would not be inclined to do for free). By contrast, an undue inducement is a genuine offer that "distorts people's reasoning abilities to such a degree that they undertake something that exposes them to unreasonable risks, the kind of risks they would not do were they more sober and reasoning clearly, or to forsake deeply held value."[197] The irresistible nature of the inducement coupled with the cognitive distortion results in acceptance of unreasonable risks.

Unlike the excessive-reward view, which speaks solely to the size and nature of the offer, the Emanuel account of undue inducement has the advantage of speaking to how the offer affects the target (i.e., the potential research participant). Emanuel writes that

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[195] Emanuel, *supra* note 189, at 100.

[196] Emanuel, *supra* note 19, at 9.

[197] *Id.*

"[i]nducements prompt ethical concern when they distort people's judgment, encouraging them to engage in activities that contravene their interests because they are harmful."[198] Thus, his account is superior to the excessive-reward view because it clearly articulates the widely held concern that an undue inducement creates a cognitive distortion that impacts the validity of consent to enroll.[199] It also provides additional criteria that more comprehensively articulate what is wrong about undue inducement.

On our view, as on Emanuel's, if an offer of payment, even an extremely large one, simply motivates people to enroll in research when they otherwise would not—and does not distort their perception of the risks—then it is a *mere* inducement and not an *undue* one.

> Given that inducement is a common element of human life, it seems difficult to see what would be uniquely worrisome about inducement in research. Working life often involves inducements and in particular sometimes involves inducements for engaging in risky working behavior (so-called "danger money"). . . . If we are to complain about inducement in research, it seems apt to consider it elsewhere as well.[200]

Thus, without research exceptionalism, it is difficult to show that anything is wrong with the use of offers of payment merely to induce participation in research. In contrast, it is consistent with views of offers of payment outside of research to be concerned when amounts are so high as to cause people to behave irrationally in ways that could result in unreasonable harm.

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[198] Emanuel, *supra* note 189, at 100.

[199] *See, e.g.*, U.S. DEP'T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993) (warning that offers that are " too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment'' about the risks of participation in research). Wertheimer & Miller, *supra* note 173, at 391.

[200] Wilson & Hunter, *supra* note 114, at 50.

According to Emanuel, "[u]ndue inducement cannot occur in otherwise ethical clinical research because there is no possibility of excessive risks, of assuming risks a reasonable person would not assume."[201] This is because IRB approval is conditioned on a determination that a study has a favorable risk-benefit ratio, completely independent of any offer of payment, and a person could reasonably decide to participate.[202] IRBs "are required to determine that any risks of serious harm are *offset or outweighed* by either the prospect of individual benefit or by the value of the knowledge that the trial is designed to generate."[203] Even when the social value of a proposed study is very high, IRBs must ensure that risks to individual participants have been minimized. Thus, once a protocol has been approved by an IRB, it is essentially by definition a reasonable proposal to put before potential participants.

Nonetheless, because an IRB is approving a protocol for a *general* population, and not evaluating the circumstances of *individual* participants, it remains possible that in some cases, an individual's particular circumstances might make his or her participation in an approved study unreasonable, i.e., the result of bad judgment. In other words, it is possible that participation is not in the individual interest of any particular research participant. One might, for example, think of a devout Jehovah's Witness who is considering participating in an IRB-approved study that requires receiving a blood transfusion because

[201] Emanuel, *supra* note 19, at 11.

[202] *Id.*

[203] Alex John London, *Undue Inducements and Reasonable Risks: Will the Dismal Science Lead to Dismal Research Ethics*, 5 AMERICAN JOURNAL OF BIOETHICS 29, 29 (2005).

it is high paying.[204] For this reason, we do not ascribe to Emanuel's view that undue inducements *cannot* occur in otherwise ethical research.

However, we do think they are *extremely unlikely* to occur. This is because situations in which an individual's interests may be so unique as to fall completely outside of the risks and benefits evaluated by the IRB are likely to be rare. A default position of encouraging highly restrictive approaches to offers of payment in research—intended to forestall undue inducements—are, therefore, inappropriate if IRB review functions as intended, i.e., as a bulwark against unethical research.

3. Coercive Offers

Professor Joan McGregor flatly rejected Emanuel's four-part definition of undue inducement as "wrong."[205] She countered, "Only the first condition from his list, that a good is offered in exchange for something, is necessary for undue inducement. The other conditions are too vague to be useful or are clearly not necessary conditions."[206]

McGregor instead favors defining undue inducements as "coercive offers."[207] This seemingly eliminates undue inducement as a distinct concept and places McGregor back in the discussion of coercion above. From McGregor's perspective, the prohibition against

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[204] Jehovah's Witnesses, *Why Don't Jehovah's Witnesses Accept Blood Transfusions?*, https://www.jw.org/en/jehovahs-witnesses/faq/jehovahs-witnesses-why-no-blood-transfusions/ (last visited Feb. 16, 2016).

[205] Joan McGregor, *"Undue Inducement" as Coercive Offers*, 5 AMERICAN J. OF BIOETHICS 24, 25 (2005) (suggesting that Emanuel's account fails to capture our intuitions about Joel Feinberg's "lecherous millionaire" example, in which a millionaire offers to pay for a sick boy's medical care if his impoverished mother will be the millionaire's mistress).

[206] *Id.*

[207] *Id.*

undue inducements is intended to guard against taking advantage of vulnerable populations, including impoverished persons with few, if any, alternatives.[208] Note the similarity of this position to the view of coercion as simply having no reasonable alternative. For reasons discussed above, we find this definition untenable.

4. Empirical Evidence of Undue Inducement

Once undue inducement is defined to include distortion of a person's rational risk assessment as a necessary condition, we have an empirical question: does such distortion actually occur in practice? Importantly, available empirical research suggests that it may not. To the contrary, some studies indicate that offers of payment draw prospective research participants' attention to risks (rather than causing risks to be ignored), while other studies have found no association between offers of payment and perceived research risk.

Cynthia Cryder and colleagues found that while higher offers of payment increased willingness to participate, these offers also increased perceived risk and the time spent reviewing information about research-related risks.[209] Jacquelyn Slomka and colleagues conducted in-depth interviews with individuals taking part in three HIV prevention studies.[210] While the interviewees saw money as a necessary incentive to attract research participants, at least some expressed a belief that large financial incentives might raise

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[208] *Id.*

[209] Cynthia E. Cryder, Alex John London, Kevin G. Volpp, & George Lowenstein, *Informative Inducement: Study Payment as a Signal of Risk*, 70 SOCIAL SCIENCE & MED. 455 (2010).

[210] Jacquelyn Slomka, Sheryl McCurdy, Eric A. Ratliff, Sandra Timpson, & Mark L. Williams, *Perceptions of Financial Payment for Research Participation among African-American Drug Users in HIV Studies*, 22 J OF GEN. INTERNAL MED. 1403 (2007)

concerns about risks.[211] Scott Halpern and colleagues found that, although higher payment motivates research participation, there was no evidence that higher payments altered patient's perceptions of the risks of research participation, that is, their comprehension.[212] John Bentley and P.G. Thacker determined that higher levels of payment increase willingness to participate, but, perhaps counterintuitively, there was no association between monetary payment and perceived risk.[213] Finally, Eleanor Singer and Mick Couper conducted an online vignette-based survey and concluded that while larger incentives induced greater overall participation, "respondents do not appear to exchange higher incentives for greater risks."[214] Although more data are needed, these studies do not indicate that higher payment necessarily or even frequently leads to cognitive distortion regarding the risks of research participation.

That said, however, empirical evidence does suggest that undue inducements may prompt research participants to lie, deceive, or otherwise conceal information from investigators.[215] Some individuals interviewed by Slomka and colleagues "believed that if a

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[211] *Id*. at 1405–1406 ("In response to questions about monetary influences on risk assessment, some respondents said they would participate in a study if the price was right in spite of the risks, whereas others said they would decline certain risky studies no matter what amount of money was offered.").

[212] Scott D. Halpern, Jason H.T. Karlawish, David Casarett, Jesse A. Berlin, & David A. Asch, *Empirical Assessment of Whether Moderate Payments are Undue or Unjust Inducements for Participation in Clinical Trials*, 164 ARCH INTERN MED. 801, 803 (2004).

[213] John P. Bentley & P.G. Thacker, *The Influence of Risk and Monetary Payment on the Research Participation Decision Making Process*, 30 J. MED. ETHICS. 293, 296–297 (2004).

[214] Eleanor Singer & Mick P. Couper, *Do Incentives Exert Undue Influence on Survey Participation? Experimental Evidence*, 3 J. EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS 49, 53 (2008).

[215] Investigators who responded to our pilot survey, described in Part V, raised this as a concern. For example, one respondent explained: "Recruiting through Craigslist or other online methods seems to draw a lot of people who are unduly influenced by the compensation, to the point that they will lie about their medical history." Another stated, "'Professional subjects' are very problematic for us. They lie during the screening process in order to get into the study, they have poor compliance, and their data messes up our

large amount of money was offered, individuals would be more likely to provide false information to investigators and 'say anything' to obtain the money."[216] Bentley and Thacker's study "showed that higher levels of monetary payment may influence subjects' behaviors regarding concealing information about restricted activities."[217] They expressed concern that "[I]f such activities were actually engaged in, the results of the hypothetical studies may have been distorted."[218] In our view, this act of deception may indicate a distorted understanding of risks or an unreasonable willingness to assume risks of participation, for example, by circumventing exclusion criteria or lying about adverse events that could lead to disqualification. Thus, some concern about undue inducement in practice remains.

Nonetheless, we note that "[w]orkers may lie about their qualifications too, in ways that put both themselves and their employers' output in jeopardy, and they may be enticed to do so by money."[219] Without research exceptionalism, the fact that highly-compensated research participants might be more likely to lie than unpaid or less-compensated research participants cannot justify a limit on compensation to research participants but not for other jobs. The immediate response to deceit by research participants should not be to reduce payment. Regulatory oversight bodies, sponsors, and investigators "could implement national subject registries to track participants [to avoid duplicative enrollment

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findings. For this reason, we compensate as little as possible, to decrease the number of these subjects that we enroll."

[216] Slomka, McCurdy, Ratliff, Timpson, & Williams, *supra* note 210, at 1406.

[217] Bentley & Thacker, *supra* note 213, at 297.

[218] *Id.*

[219] Lynch, *supra* note 42, at 162.

for financial gain], . . . utilize more extensive screening before enrollment [to better check against inclusion/exclusion criteria], and increase use of physical testing rather than relying on qualitative subject feedback whenever possible."[220] In some instances, it may be necessary to limit payment to avoid the problems entailed by deceitful research participants, but these cannot justify blanket limits on offers of payment in all clinical research.

C. The Relationship Between Coercion and Undue Inducement

On one view, coercion and undue inducement are not distinct concepts, but rather fall on a sliding scale, with one being a more extreme version of the other. This view purports that the "quantity of payment is directly correlated with the 'pressure' on the decision-maker, and the threshold of pressure necessary to constitute undue influence is less than the threshold of pressure necessary to constitute coercion."[221] The sliding scale view is intuitively appealing and may be implied by some of the leading regulatory and ethical guidelines, like the U.S. Common Rule, which mention coercion and undue inducement together and do not draw a clear conceptual distinction between them.[222]

Nevertheless, we join others in forcefully arguing for distinguishing undue inducement and coercion as distinct concepts. Emanuel, for instance, contends that "[u]ndue inducement is the diametric opposite of coercion. While both make a person do what may be unethical, illegal, or imprudent, the former dangles a good, a positive offer to

[220] *Id.* (internal citations omitted).

[221] Largent, Grady, Miller, & Wertheimer, *supra* note 24, at 506.

[222] *Id.*

induce bad judgment that leads to harm, while the latter entails an overwhelming threat. . . . Coercion requires a threat of what the person considers a worse consequence, while undue inducement offers a positive good."[223] Additionally, whereas undue inducement compromises the validity of consent by creating a cognitive distortion and impairing comprehension, coercion compromises the voluntariness of consent by the threat of harm.[224]

Additional support for the argument that these are distinct concepts may be found in the legal rules, or canons, of statutory interpretation. It is a "cardinal principle of statutory construction that a statute ought, upon the whole, to be so construed that, if it can be prevented, no clause, sentence, or word will be superfluous, void, nugatory, or insignificant."[225] In the case of the Common Rule, quoted above, this would favor understanding coercion and undue inducement as distinct concepts, rather than one as an extreme form of the other.

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In this section, we have illustrated the lack of definitional consensus within the bioethics community pertaining to coercion and undue inducement. The conceptual definitions are highly variable, and as a result, different individuals reviewing an offer of

[223] Emanuel, *supra* note 19, at 101 ("The 'your money or your life' threat of coercion is clearly different from the $1 million offer of undue inducement.").

[224] Largent, Grady, Miller, & Wertheimer, *supra* note 24, at 506. *See also* Wilkinson & More, *supra* note 185, at 378 (1997) ("Coercion is paradigmatically a case of the denial of autonomy, since it consists in the deliberate imposition of one person's will on another. However, coercion usually takes the form of threats, which restrict people's options. Inducements are offers, not threats, and they expand people's options.").

[225] 82 C.J.S. Statutes § 433. Disregarding surplusage.

payment may reach different conclusions in practice about whether that offer is coercive or unduly influential, and in turn, whether it is ethically permissible or impermissible. Moreover, it is easy to see that, depending on how two individuals define the respective terms, they could talk past one another. They may be using the same term to refer to different ethical concerns; different terms to refer to the same concern; or different terms to refer to different concerns.

Clearly, it is desirable for the human subjects research community to come to consensus on what these terms mean. We have argued that once one rejects research exceptionalism, certain definitions come to the fore. Yet, even if one continues to defend research exceptionalism with regard to payment, it is possible to endorse our preferred definitions on the grounds of their superior explanatory power and consistency with the canon of non-surplusage.

V. Case Study: Confusion in Practice

As the preceding sections have highlighted, it is reasonable to expect that the lack of substantive guidance regarding offers of payment from key regulatory agencies and other influential bodies in research ethics, the misguided tendency toward research exceptionalism, and the want of clarity about how to define coercion and undue influence will result in conceptual confusion among IRBs and investigators, as well as a general trend toward conservative approaches to payment. In this section, we present preliminary research that illustrates precisely such confusion and an emphasis on protecting subjects from payments that are deemed to be "too high." The purpose of this case study is to show

that the challenges identified herein are not just theoretical, but can have concrete effects in practice.

A. Institutional Guidelines

IRBs—and the institutions with which they are affiliated—have wide discretion when it comes to overseeing offers of payment made to research participants. As a result, one finds predictably wide variation in institutional policies. As part of this project, we reviewed payment-related policies for all of the IRBs affiliated with Harvard Catalyst. Harvard Catalyst, Harvard's Clinical and Translational Science Center, is part of the National Clinical and Translational Science Award (CTSA) consortium[226] and "works with Harvard schools and the academic healthcare centers (hospitals) to build and grow an environment where discoveries are rapidly and efficiently translated to improve human health."[227]

In 2015, we reviewed official copies of policies and guidelines regarding payment of research participants for each of the Harvard Catalyst-affiliated institutions.[228] Although we do not suggest that these institutions provide a representative sample of research institutions across the country, they do range from world-renowned academic medical centers to local community hospitals. Because the goal is simply to demonstrate variety,

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[226] Sixty medical research institutions are members of the CTSA Consortium, which is funded by the National Center for Advancing Translational Sciences (NCATS), a part of the National Institutes of Health (NIH). HARVARD CATALYST, *National CTSA Consortium*, http://catalyst.harvard.edu/about/consortium.html.

[227] HARVARD CATALYST, *About Harvard Catalyst*, http://catalyst.harvard.edu/about/ (last visited Feb. 1, 2016).

[228] There are thirty-one participating institutions. *Id.*

rather than to praise or criticize any institution's policy, we refrain in this discussion from attributing particular policies to particular institutions.[229]

Several of the Harvard Catalyst-affiliated institutions share umbrella IRBs (and therefore were covered by a single policy). In all, six institutions had no policy governing offers of payment to research participants, whereas 13 IRBs (covering the remainder of the participating institutions) did have a payment-specific policy or policies.[230] Of those with policies, there is a great deal of heterogeneity: whereas some largely parrot the regulations, others go into much more extensive detail.

When an institution has a policy regarding offers of payment to research participants, that policy can reasonably be expected to establish the default for how payment is viewed by both IRB members and investigators. Two policies were particularly striking in their contrast. The first of these stated: "It is sometimes desirable to provide payments to subjects and their families for their participation in research projects."[231] By contrast, the second stated:

> It is not necessary, required, or desirable that all subjects involved in clinical research receive monetary compensation for their participation. Some subjects derive medical benefit as a result of their participation; some subjects volunteer out of sheer altruism . . . or for other personal reasons.[232]

The former sets a default that is much more favorable to offers of payment than the latter, and also seems to be more in line with approaches to payment that might be expected

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[229] Policies are on file with the authors.

[230] This is consistent with the findings presented in Neal Dickert, Ezekiel Emanuel, & Christine Grady, *Paying Research Subjects: An Analysis of Current Policies*, 136 ANN. INTERN. MED. 368, 369 (2002).

[231] Institution A.

[232] Institution B.

outside of the research context, whereas the latter appears to be influenced by research exceptionalism.

In reviewing these policies, we observed several trends relevant to our present discussion. First, and most notably, the vast majority of policies do not include definitions of either coercion or undue inducement, despite (or perhaps because of) the fact that these terms are not clearly defined in the U.S. federal regulations, nor are there broadly accepted definitions in the research ethics literature. There were two notable exceptions. The first defines coercion, roughly correctly, as "undue pressure."[233] The second, however, suggests coercion means "unduly inducing individuals to participate because compensation would be difficult to refuse."[234] Not only is this definition of coercion clearly incorrect on our preferred definitions, it mistakenly conflates coercion with undue influence, suggesting the terms are interchangeable when they are correctly understood as distinct.

Second, the policies reviewed also reflected the widespread—albeit mistaken on our view—belief that offers of payment can be coercive. One policy states, for instance: "Payment should not be coercive."[235] Another explains, "When subjects are being paid, the [IRB] will review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive."[236] A third states, "The IRB reviews remuneration plans to assess whether the amount, schedule and type of any proposed

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[233] *Id.*

[234] Institution F. Undue influence was never defined by this policy.

[235] Institution L.

[236] Institution K.

compensation . . . could be considered coercive."[237] As we have stressed above, genuine offers of payment are never coercive because they do not threaten to violate an individual's rights but instead expand an individual's options.

Third, the policies generally allowed advertisements to indicate that payment would be offered, as long as undue emphasis was not placed on the offer of payment.[238] A typical policy stated, "[A]dvertisements *may* state that Human Subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type."[239] None of the polices we reviewed expressly forbade inclusion of payment nor did they require that offers of payment be explicitly mentioned in the advertising materials. While the policies do not explicitly link limits on advertising to either coercion or undue inducement, presumably such limits are motivated by a fear that research participants could be inappropriately influenced to participate in research by an emphasis on payment in advertising materials. Given our view on the broad acceptability of offers of payment made to research participants, we believe policies that allow inclusion of reasonable information about payment at the investigators' discretion are not only appropriate, but ideal.

Of course, we understand the difficulty of drafting these policies in the absence of clear regulatory guidance and the presence of robust academic debate. The confusion they reflect is reasonable given the confused circumstances from which they emerge. Ideally, however, institutions would bridge the gap between policy and practice, defining crucial

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[237] Institution F.

[238] *See generally*, Megan S. Wright & Christopher T. Robertson, *Heterogeneity in IRB Policies with Regard to Disclosures About Payment for Participation in Recruitment Materials*, 42 J.L. MED. & ETHICS 275, 375–376 (2014).

[239] Institution C (emphasis added).

terms and providing substantive guidance on ethically acceptable offers of payment that could guide investigators and IRB members as they design and evaluate offers of payment made to research participants. There is, as we have shown, an unfortunate divergence between the ideal and reality. While this divergence is neither unexpected nor blameworthy, the lack of clear institutional guidance, layered upon a lack of clear regulatory guidance, likely reinforces a tendency toward conservative approaches to payment among IRB members and investigators.

B. Individual Survey Data

In addition to review of institutional policies, we conducted pilot surveys of individuals at Harvard Catalyst-affiliated research institutions in order to develop preliminary data about attitudes of both IRB members and investigators regarding payment generally, and about their beliefs regarding coercion and undue inducement in particular. This is the first survey to assess how investigators, as opposed to IRB members alone, define these terms.

1. Methods

Two online surveys were conducted. The first (hereafter, the "IRB Survey") was sent to IRB members and administrators and was distributed via the Harvard Catalyst Regulatory Committee, which "is comprised of institutional officials, compliance officers, and directors of human research protections from Harvard Catalyst-participating

institutions."[240] The second survey (hereafter, the "Investigator Survey") was sent to investigators and study coordinators and distributed via the Harvard Catalyst Clinical Research Center (HCCRC) email list.[241]

Two draft survey instruments, one for IRB members and one for investigators, were developed using an iterative process that began with a comprehensive review of the literature on coercion and undue inducement and offers of payment to research participants and included several rounds of revision based on input from IRB members, administrators, and experts on the ethics of human subjects research. Because much of our work was exploratory in nature, we used a combination of open- and close-ended questions. The draft surveys were pretested with IRB members, administrators, and investigators who were asked to comment on the content and design of the survey. Feedback was incorporated to refine and clarify survey items. The Investigator Survey was finalized after we had the results from the IRB Survey, and several additional changes were made to further enhance clarity.[242]

Potential participants received an email embedded with an HTML link to the confidential, self-administered survey instrument, which was administered in Qualtrics, a web-based survey tool. Two subsequent reminder emails were sent. Responses received by June 1, 2015 were included in our analysis. This project was approved by the Committee on the Use of Human Subjects, the IRB for Harvard University's Cambridge campus. No compensation was provided to participants.

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[240] Harvard Catalyst, *Regulatory Foundations, Ethics, and Law Program*, https://catalyst.harvard.edu/programs/regulatory/howwework.html.

[241] Harvard Catalyst, *Harvard Catalyst Clinical Research Center (HCCRC)*, https://catalyst.harvard.edu/programs/hccrc/.

[242] Survey instruments on file with the author.

Because this study was designed as an exploratory analysis, we summarized data using frequency distributions and descriptive statistics. We evaluated associations between responses using simple frequencies and evaluated the interrelationships between survey response items using cross-tabulations without adjustment for multiple comparisons. Statistical significance by chi-square test was defined as $p < 0.05$.

2. Results and Analysis

Of the 694 emailed invitations to participate in the IRB survey, 116 surveys were completed, for a response rate of 16.7%.[243] Of the 1,596 emailed invitations to participate in the investigator survey, 115 surveys were completed, for a response rate of 7.2%.[244]

Respondents who provided demographic information were predominately non-Hispanic white (90%) and female (62%), with a mean age of 54 (±13) for IRB members and administrators and a median age of 41-50 for investigators.[245] The majority (76%) of respondents held a masters, doctorate, or professional degree. Those with experience serving on an IRB had an average of 8 (±6) years of experience, and all but 7% said that their IRB reviewed biomedical research. Investigators reported submitting an average of 14 (±20) protocols to their current IRB. All respondents held a role or roles related to human subjects research (see Table 1).

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[243] Some of the IRBs made the members' emails publicly available or shared them upon request; in other cases, the IRB chair agreed to forward our emails. As we did not send all of the email invitations directly, we are unsure how many emails were returned as undeliverable and how many emails were forwarded without notifying us of that fact. Therefore, the adjusted response rate may differ.

[244] As we did not send any of these email invitations directly, we are unsure how many emails were returned as undeliverable. Therefore, the adjusted response rate may be higher.

[245] The CUHS asked us to change how we asked questions about age between the two studies, which is why the results are reported differently.

Table 1.
Respondents' Current Roles Related to Human Subjects Research

Role[1]	*Frequency*	*Percent*
Researcher	85	36.8%
IRB Member	91	39.4%
Study Coordinator	54	23.4%
Research Nurse	6	2.6%
Clinician, Non-Researcher	14	6.1%
Professor	39	16.9%
Ethicist	8	3.5%
Sponsor	3	1.3%
Regulator	4	1.7%
Subject Recruiter	11	4.8%
Evaluate Grants	14	6.1%
Write Policy	16	6.9%
Member of Human Research Protection Program	14	6.1%
Other Study Staff	10	4.3%
Other	16	6.9%

[1]Respondents could choose more than one role

Beyond these demographics, however, we will generally present the results for investigators and IRB members together because there were few instances in which the differences in their answers reached statistical significance; where the difference was statistically significant, we have included a footnote indicating that to be the case. This is an interesting finding in itself because it shows that IRB members and investigators are confused in similar ways, as explored below.

Respondents were asked to select which of a given series of definitions properly defined coercion, and were permitted to select more than one option; we did not, however, indicate which definition reflected our preferred view. See Table 2. Nearly all respondents agreed that a research participant is coerced if threatened with harm or loss of benefits to

which he is otherwise entitled if he doesn't participate in research (87.0%),[246] a definition consistent with the rights-violating view of coercion we endorse. The vast majority also agreed that a research participant is coerced if he participates as the result of intimidation, or some other form of pressure or force (90.0%), consistent with the worse-off view. While we favor the rights-violating view, for reasons discussed above, there is often little difference between the two views in practice. These results are encouraging in the sense that they indicate that most respondents include the correct (by our analysis) definitions of coercion in their understanding of the term.

Less encouraging, however, is that respondents might also be including incorrect definitions. A majority agreed that a research participant is coerced if the offer of payment causes him to feel he has no reasonable alternative but to participate in research (71.0%), if the offer of payment distorts his ability to perceive accurately the risks and benefits of research (63.6%),[247] or if the offer of payment makes him participate in research he would not otherwise participate in (51.1%). From our perspective, that a majority of respondents would endorse these definitions demonstrates a widespread and fundamental misunderstanding of what coercion is. With respect to the first option, although some ethicists defend the no-reasonable-alternative view of coercion, we indicated above why this approach is inconsistent with understandings of what counts as coercive outside of the research context, and why it must be rejected as an instance of inappropriate research exceptionalism. The second option, that offers of payment may distort comprehension of

[246] Investigators were significantly more likely than IRB members ($p < 0.05$) to say that a research participant was coerced if threatened with harm or loss of benefits to which he is otherwise entitled (92.2% vs. 81.7%). Thus, investigators were more likely to get it right on our view.

[247] Investigators were significantly more likely than IRB members ($p < 0.05$) to say that a research participant was coerced if an offer of payment distorts the research participant's ability to perceive accurately the risks and benefits of research, which is part of our definition of undue inducement (75.9% vs. 51.3%).

risks and benefits is the correct definition for undue inducement, not for coercion. This illustrates how the two terms are often conflated. Finally, the third option is consistent not with coercion but with an ethically unproblematic *mere* inducement. More than two-thirds (68.6%) of respondents agreed with the following statement, which we view to be false: "Offers of payment can be coercive."

Next, respondents were given the same series of definitions and asked which defined undue influence. See Table 2. Three-quarters (74.5%) of respondents agreed that a research participant is unduly influenced if the offer of payment distorts his ability to perceive accurately the risks and benefits of research, which means that a full quarter of respondents failed to identify what we view to be the correct definition of undue inducement. It is perhaps most worrisome that more than half of the respondents (58.9%) agreed that research participants are unduly influenced if the offer of payment makes them participate in research they would not otherwise participate in. Again, this seems more accurately to describe a mere inducement (i.e., something that one would not otherwise have done), not one that is *undue per se*, and is an expansive view potentially at odds with the pervasive use of offers of payment as an incentive for participation in research.

In these numbers, we again see evidence that IRB members and investigators often conflate undue influence and coercion. The majority agreed that research participants are unduly influenced if they participate as the result of intimidation, or some other form of pressure or force (60.6%)[248] or if they are threatened with harm or loss of benefits to

[248] Investigators were significantly more likely than IRB members ($p < 0.05$) to say that a research participant was unduly induced if she participates as the result of intimidation, or some other form of pressure or force (69.8% vs. 51.3%), which is instead one of our definitions of coercion.

which they are otherwise entitled if they do not participate in research (55.8%),[249] both of which are definitions applicable instead to coercion.

Table 2.
Definitions of Coercion and Undue Inducement

% of respondents who agreed that if . . .	Then . . . *it is coercion*	Then . . . *it is undue inducement*
The research participant is threatened with harm or loss of benefits to which he is otherwise entitled if he doesn't participate in research	87.0%	55.8%
The research participant participates as the result of intimidation, or some other form of pressure or force	90.0%	60.6%
The offer of payment makes the research participant participate in research he would not otherwise participate in	51.1%	58.9%
The offer of payment distorts the research participant's ability to perceive accurately the risks and benefits of research	63.6%	74.5%
The offer of payment causes the research participant to feel he has no reasonable alternative but to participate in research	71.0%	69.3%

Undue inducement and coercion are often said to be conflated,[250] a claim consistent with our findings. Our data suggest that people use these terms somewhat

[249] Investigators were significantly more likely than IRB members ($p < 0.05$) to say that a research participant was unduly induced if threatened with harm or loss of benefits to which they are otherwise entitled (64.7% vs. 47.0%), which is instead one of our definitions of coercion.

[250] *E.g.*, Ezekiel J. Emanuel, Xolani E. Currie, and Allen Herman, *Undue Inducement In Clinical Research in Developing Countries,* 366 LANCET 336, 337 (2005) (describing how it is not unusual for undue inducement to be "conflated with coercion, exploitation, injustice, deception, misunderstanding, and other ethical transgressions as if they were equivalent or interchangeable").

interchangeably. Some individuals chose the same definitions for both coercion and undue inducement. Moreover, a majority of respondents (65.2%) agreed with the statement that "coercion is an extreme form of undue influence," consistent with the "sliding scale view" and demonstrating a failure to appreciate that coercion and undue inducement are distinct concepts.[251]

3. Limitations

This was an exploratory study without a nationally representative sample and with a low response rate, which imposes limits on the conclusions we can draw. While the respondents are professionally diverse and have considerable experience in human subjects research, they may have views that differ from others involved in the research enterprise, especially given that our results were generated exclusively from Harvard Catalyst-affiliated research institutions. Yet, as mentioned above, Harvard Catalyst encompasses institutions ranging from academic medical centers to community hospitals to schools of medicine and public health.

Another limitation to this exploratory data is that we asked about concepts only in the abstract, rather than including case studies. Thus, it is possible that even if IRB members and investigators adopt overly expansive definitions of coercion and undue inducement when asked about these terms in the abstract, these definitions have little impact on their decisions to approve or not approve offers of payment in specific instances. Yet, the federal Common Rule requires investigators to seek informed "consent only under

[251] Largent, Grady, Miller, & Wertheimer, *supra* note 24, at 506.

circumstances that minimize the possibility of coercion or undue influence,"[252] and OHRP cautions investigators and IRBs to "be vigilant about minimizing the possibility of coercion or undue influence."[253] Therefore, although more research is needed, we hypothesize that these confused views *do* influence how IRBs interpret offers of payment as well as how investigators structure offers of payment.

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In response to our pilot survey, some IRB members and investigators readily admitted to their confusion,[254] and many others showed themselves to have a faulty conceptual understanding of coercion and undue inducement on our preferred definitions. Some respondents identified the best definitions while also endorsing incorrect views, suggesting that their understanding of these concepts is overly expansive. In some instances, respondents identified a legitimate ethical concern but called it by the wrong name. In other instances, they expressed concern about something that is not a legitimate ethical concern at all, but called it by an ethically charged name.

As a result, we fear that IRBs sometimes incorrectly reject offers of payment that really ought to be ethically acceptable, thereby eliminating a potentially important tool in clinical trial recruitment. The flip-side of this is that investigators share many of the

[252] *Id.* at § 46.116.

[253] OHRP, *What does it mean to minimize the possibility of coercion or undue influence?*, http://www.hhs.gov/ohrp/policy/faq/informed-consent/what-does-coercion-or-undue-influence-mean.html.

[254] For instance, a handful (5%) of respondents to the IRB survey explicitly stated that they were not certain how to define undue influence in answer to a free response question.

misconceptions that IRB members have—not only do investigators have the same dearth of guidance on what these terms mean, they may also be reliant on the IRB to guide them in how to understand and apply these terms. As a result, they may not submit protocols with offers of payment that they expect will be met unfavorably by the IRB, or may fail to advocate for offers of payment once the IRB has questioned them, even when those payments really ought to be viewed as ethically acceptable.

VI. Implications for Policy and Practice: The Path Forward

Given the potential for confusion and conservative approaches to payment demonstrated above, it is clear that something must be done. Here, we will consider several possible solutions to the problems we have identified.

A. If Not Accuracy, Precision

In the field of science, accuracy tells us how close a measurement is to the true value. Precision, by contrast, refers to the closeness of two or more measurements to each other.[255] Unfortunately, our data suggests that currently when IRB members and investigators define and use the terms coercion and undue inducement, they are often neither accurate nor precise. While we have argued above for the definitions that we think are best, we also recognize that reasonable disagreement is possible. In the face of disagreement among ethicists about what each of these concepts mean, it seems

[255] Imagine you have a box that you know weighs exactly 10 pounds. You take it home and weigh it five times on your bathroom scale. Each time, the scale says that the box weighs 7.5 pounds. Your scale is precise because it said that the box weighed 7.5 pounds each time, but your scale is not accurate because 7.5 pounds is not close to the known value of 10 pounds.

unrealistic—at least in the absence of a definitive statement from OHRP or FDA, which we discuss below—to ask that IRB members and investigators universally accept one meaning as factually correct. Therefore, accuracy might be too much to hope for, but precision is not.

How might we achieve precision? As a first step, we propose relying much less on these labels to do the heavy-lifting. It appears from our data and some strands of the bioethics literature that the terms coercion and undue inducement may be used as "catchalls" when something about research (e.g., an offer of payment) seems somehow not right. Because most everyone agrees that coercion and undue inducement in the context of human subjects research are wrong, use of these terms can be a conversation killer and result in not approving a protocol or an aspect of a protocol. Yet, to the extent that people understand these terms expansively or understand them in wildly ways, people may well be talking past one another when these terms are used. Therefore, leveling the charge that a research protocol—and particularly an offer of payment—is coercive or unduly influential should be the beginning, rather than the end, of the conversation. Individuals interested in protecting research participants should explain *precisely why* they think that a particular research proposal is problematic rather than assuming that the label alone does sufficient explanatory work, or that the label itself will carry the same meaning for the listener as it does for the speaker.

So, for example, instead of saying that a proposed offer of payment would create undue inducement, it would be vastly preferable to say that a proposed offer of payment appears so high that it might prevent prospective research participants from adequately evaluating the risks and burdens of enrolling in the associated trial, while also offering

specific evidence for why that worry is present in this particular case. Employing that level of specificity will limit the extent to which individuals talk past each other and allow the conversation to focus on the ethical concern at hand. To continue with the example, once the concern is expressed as money impinging on the evaluation of risks, it is possible to have a substantive discussion about whether the offer of payment is so high that it predictably creates a cognitive distortion, whether the research is otherwise ethical such that a reasonable person could agree to participate, or whether additional safeguards are needed for the informed consent process. Such questions would, for example, have been useful to assess prospectively the offer of payment made to research participants in France.

B. Changing the Default Rules to Favor Payment

As described above, we think that research exceptionalism is generally wrongheaded when it comes to offers of payment, and that offers of payment do not need to be subjected to greater scrutiny in the research context than elsewhere. If so, that is a strong argument in favor of changing the default to generally accept offers of payment to research participants unless there is compelling evidence that they are harmful. Even if one continues to accept some form of research exceptionalism, if coercion and undue inducement are not actually happening in practice when payment is offered to participants, then we are making mountains out of molehills when we set the default in favor of low (or no payment).

We have argued that coercion is incorrectly associated with genuine offers of payment. While undue inducement is a more credible concern when offers of payment are extended to research participants, we caution that there is little evidence that undue

inducement is occurring in practice. As described above, empirical research has failed to substantiate the claim that offers of payment lead to irrational choices by research participants. In fact, some scholars have found that offers of payment heighten subjects' attention to the risks and burdens of research participation. We suggest that many regulators, IRBs, investigators, and other stakeholders in human subjects research are, therefore, inappropriately concerned about offers of payment being too high. Offers of payment, even extremely high ones, should not generally be cause for ethical concern.

From our perspective, the larger concern is that subjects may be inadequately compensated for their contribution to socially beneficial research, which may slow recruitment, hinder retention, or exploit research participants who are not paid enough. Alan Wertheimer's account of exploitation has been both admired and adopted by many. According to Wertheimer, to exploit someone is to take *unfair* advantage of him or her.[256] Exploitation occurs when, due to an asymmetry of bargaining power, one party to a transaction insufficiently benefits or assumes an unfair share of the burden relative to other parties to the transaction. This suggests that a default in favor of payment is preferable to a default against payment.

At a minimum, individuals "should not have to pay for making a contribution to the social good of research."[257] This entails providing reimbursement for any research-related expenses they incur and adequate compensation for research participants' time and effort, as well as risks they willingly incur as a result of their participation in research. Such offers of payment demonstrate respect for research participants, and treat them in accordance to

[256] ALAN WERTHEIMER, EXPLOITATION (Princeton: Princeton University Press, 1996).

[257] CIOMS, *supra* note 110, at n.p.

what would be expected outside the research context. In some studies, acceptable offers of payment may be *de minimus* (e.g., a study that consists of a one-time blood draw), but in other studies, the minimum acceptable payment may be substantially higher.

Additionally, offers of payment can unproblematically be used to incentivize research participation. We think it is fundamentally wrong to argue, as some have, that "the need for large incentives can be a rough indicator that there may be an ethical concern that requires attention."[258] People may simply wish to avoid the discomfort or burdens of research participation, and just as incentives are acceptable in other areas of life to override such reluctance, they are acceptable in the context of human subjects research—particularly if one accepts, as we do, the role of the IRB in determining that the risks of a study are reasonable in relation to the benefits, either to the individual or to society.

We do note that some people worry "that poverty or otherwise compromised circumstances may force people to take an inducement that people in a better situation shun."[259] This concern is often raised when research is conducted in developing countries, but its application is not geographically limited. Yet, "tempting offers in desperate situations that have clear good results are not undue inducements"[260] because accepting such an offer can be a reasoned judgment that does not necessarily contradict one's interests. It is an unfortunate consequence of research exceptionalism to frame these offers as undue inducements, and it would be unacceptably paternalistic to protect competent research participants from their fully voluntary and rational undertakings.

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[258] Grant & Sugarman, *supra* note 19, at 734.

[259] Ezekiel J. Emanuel, Xolani E. Currie, and Allen Herman, *Undue Inducement In Clinical Research in Developing Countries,* 366 LANCET 336, 338 (2005).

[260] *Id.*

Moreover, it is backwards to think that protecting them requires paying *less* in light of their poverty; ideally, the response should be to pay them more.

To demonstrate this point, consider that a person who is facing poverty might be willing to work as a day laborer, which may be risky and burdensome, whereas a more affluent person would not be willing to do so. Of course, this does not mean day laborers should be paid less. If we think paid day labor is acceptable, then it is an instance of research exceptionalism to suggest that paid research participation is unacceptable simply because more affluent individuals may not find participation a compelling offer, given other options they have available. The factors that lead some people to participate in research in order to earn a living or supplement their income might be circumstances we would all think of as unjust, and would prefer not to have occur, but those circumstances are not reasons to limit the options of competent adults given the realities – and other protections for research participants – that exist.

Additionally, although we do not think offers of payment are a panacea for recruitment problems, greater incentives may have the dual benefit of improving enrollment and drawing a more diverse pool of research participants (such that we are not reliant solely on people who find current, relatively low offers of payment acceptable). This could ensure that socially valuable research is completed and that the burdens of research are spread more broadly over the population.

In medicine, a false positive is an error where a result is improperly reported as positive when it actually is not. A false negative is an error where a result is improperly reported as negative when it actually is not.[261] This is contrasted with a true result: a true

[261] For example, if a pregnancy test says you are pregnant when you actually are not, that is a false positive.

positive or a true negative. The judgments of an IRB can be fallible just as medical tests can be fallible. We might equate disapproval of an offer of payment that is actually ethically acceptable with a false negative. Although our survey data do not allow us to determine conclusively how frequently this occurs, the attitudes reflected in the survey suggest that under the current scheme, there may be many false negatives.

Some false positives or false negatives may be unavoidable. One consequence of changing the default to generally accept offers of payment is that some offers of payment that are ethically concerning might get through—yet, we expect that this is only a slight possibility. We have argued that coercion and undue inducement are unlikely to occur in otherwise ethical clinical research. Given that the harms from overpayment are generally overstated, and the harms from underpayment are understated, we advocate changing the default rules so that offers of payment will be deemed acceptable unless someone can articulate a clear (i.e., precise) and persuasive—as opposed to speculative—reason why it is not.

C. Policy Guidance and Rulemaking

Policy guidance and educational efforts are sorely needed to clarify the concepts of coercion and undue inducement as applied to the research setting. Formal rulemaking pertaining to offers of payment seems improbable under present circumstances. Therefore, we propose that OHRP update its FAQs and that the FDA update its Information Sheet on payment to research participants. While this guidance would not be binding, as the embodiment of the agencies' current thinking, it would likely be persuasive for many IRBs and investigators.

Any such guidance should provide clear definitions of coercion and undue inducement, as well as of exploitation—a concern that is not currently addressed at all, but that we think is ethically salient, and increasingly so as more research is conducted in developing countries. We would strongly advocate for our preferred definitions. At a minimum, this guidance should clarify—by stating explicitly rather than leaving it for the reader to infer—that genuine offers of payment are never coercive and reflect the empirical evidence suggesting that undue inducement is rare. It should also emphasize the importance of offering reimbursement for research-related expenses and compensation for time, effort, and inconvenience. Ideally, the guidance would also state that use of offers of payment to incentivize research participation are generally acceptable and that payment can be used to address exploitation, or an unfair distribution of research benefits and burdens.

Conclusion

The practice of offering payment to individuals in exchange for their participation in clinical research is widespread and longstanding. Nevertheless, offers of payment to research participants remain the source of substantial debate. Two ethical charges routinely arise in relation to these offers—that they are coercive or unduly influential. Because there is general agreement that coercion and undue inducement are wrong in human subjects research, such a charge can shut down conversation among IRB members and investigators, and result in rejection of an offer of payment, or failure to make an offer in the first place.

As we have recounted, the various laws, regulations, and ethical guidelines that govern the conduct of human subjects research offer relatively little in the way of specific guidance about what factors or features characterize ethically acceptable offers of payment. Additionally, there is a lack of agreement regarding what exactly the terms coercion and undue inducement mean in the human subjects research context. It is, therefore, unsurprising that the space inhabited by IRB members and investigators is characterized by confusion and conservatism. The results of our pilot survey suggest that IRB members and investigators are worried about things that they probably do not need to be worried about. That may lead to overprotection, and possibly distraction from things they should actually be worried about—particularly the possibility that offers of payment are too low. Ultimately, resolving misplaced concerns about offers of payment being too high will offer investigators a more powerful recruitment tool and, hopefully, speed the pace of innovation and discovery.

In closing, we return briefly to France. The offer of payment to research participants was not, nor should it be construed as, a signal that the trial was otherwise unethical. Instead, as investigations into what happened move forward, attention needs to be paid to substantive questions such as whether the risks to participants were, in fact, minimized and whether the research participants gave adequately informed consent. We do not, at present, have reason to believe the offer of payment was itself unethical. Research advances the social good: we need better treatments for Parkinson's Disease and chronic pain, the conditions the novel compound BIA 10-2474 was designed to treat.

Clinical "[r]esearch is a social good . . . but there are risks . . . Being a construction worker is very risky, and we pay people to do that. So why not this?"[262]

[262] Elisabeth Rosenthal, *When Drug Trials Go Horribly Wrong*, THE NY TIMES (Apr. 7, 2006) (quoting Ezekiel Emanuel after the TeGenero trial).

EBOLA & FDA: REVIEWING THE RESPONSE TO FIND LESSONS FOR THE FUTURE

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In 2014, West Africa confronted "the largest, most severe, most complex outbreak of Ebola virus disease in history."[1] By early 2016, the total number of probable, confirmed, and suspected Ebola cases tallied since the onset of the outbreak exceeded 28,600, with 11,300 deaths.[2] The outbreak, declared a "public health emergency of international concern" (PHEIC) by the World Health Organization (WHO),[3] was difficult to bring under control owing to high infectivity, weak health systems, rampant fear and mistrust among the affected population, and fluid cross-boarder movement of peoples.[4] Although the outbreak was centered on three countries—Guinea, Liberia, and Sierra Leone—it riveted the attention worldwide of clinicians, virologists, public health experts, industry, regulators, and the lay public alike.[5]

While there are many lenses through which one might examine and critique the unfolding of and response to the 2014 Ebola outbreak, this paper adopts the lens of food and drug law and focuses on the significant role assumed by the U.S. Food and Drug Administration (FDA). Because there were no FDA-approved therapies for prevention of,

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[1] WORLD HEALTH ORGANIZATION (WHO), ETHICAL CONSIDERATIONS FOR USE OF UNREGISTERED INTERVENTIONS FOR EBOLA VIRAL DISEASE: REPORT OF AN ADVISORY PANEL TO WHO, available at http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/.

[2] WHO, WHO: EBOLA SITUATION REPORT, 6 January 2016, http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016.

[3] WHO, WHO STATEMENT ON THE MEETING OF THE INTERNATIONAL HEALTH REGULATIONS EMERGENCY COMMITTEE REGARDING THE 2014 EBOLA OUTBREAK IN WEST AFRICA, 8 August 2014, http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/. It is worth noting that this is only the third time in the agency's history that the WHO has declared a public health emergency of international concern. I.I. Bogoch, M.I. Creatore, M.S. Cetron, et al, *Assessment of the Potential for International Dissemination of Ebola Virus Via Commercial Air Travel During the 2014 West African Outbreak*, 385 LANCET 29, 29 (2015).

[4] THE LANCET, *Ebola: A Failure of International Collective Action*, August 21, 2014; Margaret Chan, *Ebola Virus Disease in West Africa—No Early End to the Outbreak*, 371 NEJM 1183, 1183–1184 (2014).

[5] For a popular account of another Ebola outbreak that captured the public imagination, see generally, RICHARD PRESTON, THE HOT ZONE: THE TERRIFYING TRUE STORY OF THE ORIGINS OF THE EBOLA VIRUS (1995).

post-exposure prophylaxis against, or treatment of Ebola virus disease (EVD), the outbreak spurred interest in developing novel treatments and vaccines; sparked calls to use experimental interventions in the field; thrust the need for human subjects research in the midst of a disaster—with the attendant practical, ethical, and methodological concerns—into the spotlight; and prompted concern about whether the worst off would ultimately have access to approved drugs and vaccines. Though geographically centered in West Africa, the EVD outbreak showcased FDA's global role in drug and vaccine development, approval, and access. Additionally, the outbreak permitted valuable lessons to be drawn regarding what FDA can do to better promote and protect public health in emergencies—whether caused by new or reemerging threats—going forward.

This is the first paper to systematically explore the role played by the FDA during the 2014 Ebola outbreak by focusing on what the FDA did in ushering new medical countermeasures,[6] particularly drugs and vaccines, to market. Section I provides background on Ebola, generally; the 2014 Ebola outbreak, specifically; and the state of vaccines against and treatments for EVD when the outbreak commenced. Section II discusses the calls that were made for use of experimental Ebola interventions in the field and outlines both the need for accreting evidence of their safety and efficacy as well as the ethical mandate to conduct rigorous human subjects research in the midst of a public health emergency. Section III briefly reviews the standard FDA-approval process and highlights challenges to the arc of development, approval, and access created by public

[6] "Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, a naturally occurring emerging disease, or a natural disaster." U.S. FOOD AND DRUG ADMINISTRATION (FDA), *What are Medical Countermeasures?*, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm431268.htm (last visited Apr. 13, 2016).

health emergencies. Next, Section IV examines how FDA responded to those challenges in the 2014 outbreak. FDA's response illustrates the panoply of tools at the Agency's disposal and its regulatory flexibility. Yet, it also reveals limitations and weaknesses. Therefore, Section IV draws lessons for the inevitable future outbreaks of emerging and re-emerging conditions—like Zika virus—for which diagnostic, prophylactic, and therapeutic interventions are inadequate.

I. Ebola Virus Disease and the 2014 Outbreak

This section offers general background on EVD, on the 2014 West African outbreak, and on the interventions available at the time of the outbreak for prevention, post-exposure prophylaxis, and treatment of EVD. An appreciation of these three strands—and how they were interwoven—is essential to understanding the calls made by prominent actors, including WHO, for use of innovative therapies in the field, discussed at length in Section II, as well as the important role played by FDA, despite it's geographic removal from the outbreak's epicenter, discussed in Sections II and IV.

A. Ebola Virus Disease

EVD was originally identified in 1976 in Zaire (now the Democratic Republic of Congo) and South Sudan.[7] It is a severe hemorrhagic fever caused by an RNA virus in the

[7] A.S. Fauci, *Ebola – Underscoring the Global Disparities in Health Care Resources*, 371 NEJM 1084, 1084 (2014).

filovrius family.[8] Signs and symptoms of Ebola—which appear anywhere from 2 to 21 days after exposure—include fever, headache, diarrhea, vomiting, muscle pain, stomach pain, and unexplained bleeding or bruising.[9] EVD is associated with a case fatality rate between 30 and 90%.[10] Diagnosis of EVD may initially be difficult, as the symptoms are nonspecific[11] and can be confused with those of diseases more common in Equatorial Africa.[12] The most useful tests for confirming an Ebola diagnosis—reverse transcriptase polymerase chain reaction and antigen detection by enzyme linked immunosorbent assay—are only available in referral centers or national reference laboratories.[13]

Outbreaks are thought to originate from an animal reservoir, most likely a fruit bat, although that linkage has not been confirmed.[14] Person-to-person infection occurs through direct contact with infected bodily fluids—usually blood, feces, or vomit.[15] As a result, most cases occur in individuals who provide direct patient-care, such as family members or

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[8] *Id*. "Ebola" encompasses five separate species—*Zaire ebolavirus*, *Bundibugyo ebolavrius*, *Taï Forest ebolavirus*, *Sudan ebolavirus*, and *Reston ebolavirus*. *Id*. Virologic investigation identified *Zaire ebolavirus* as the causative agent in the 2014 outbreak. S. Baize, D. Pannetier, L. Oestereich, et al, *Emergence of Zaire Ebola Virus Disease in Guinea*, 371 NEJM 1418, 1418 (2014).

[9] U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), *Questions and Answers on Ebola*, August 28, 2014, http://www.cdc.gov/vhf/ebola/outbreaks/guinea/qa.html; *see also* WHO EBOLA RESPONSE TEAM, *Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projection*s, 371 NEJM 1481, 1482 (2014).

[10] Baize, Pannetier, Oestereich, et al, *supra* note 8, at 1418 (noting that the case fatality rate depends on the virus species). The *Zaire ebolavirus* strain has historically resulted in the highest mortality (90%). Fauci, *supra* note 7, at 1084.

[11] Fauci, *supra* note 7, at 1084.

[12] C. del Rio, A.K. Mehta, G.M. Lyon, & J. Guarner, *Ebola Hemorrhagic Fever in 2014: The Tale of an Evolving Epidemic*, 161 ANNALS OF INTERNAL MEDICINE 746, 746 (2014).

[13] *Id.*

[14] Fauci, *supra* note 7, at 1085.

[15] *Id*.

clinicians.[16] Implementation of strict barrier and droplet precautions and use of personal protective equipment are necessary to control an outbreak.[17] When patients pass away, the body must be handled with extreme caution, and incineration is recommended.[18] Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease (NIAID), one of the institutes of the National Institutes of Health (NIH), has advised that "[a] high index of suspicion, proper infection-control practices and epidemiologic investigations should quickly limit the spread of the virus."[19]

B. The 2014 Outbreak

The 2014 outbreak began in December 2013 in Guinea.[20] The initial source of the outbreak has been identified as the village of Meliandou in Guéckédou Prefecture.[21] A young boy named Emile Ouamouno, now considered patient zero, came down with symptoms of EVD[22] and died on December 28, 2013.[23] Members of his family, a nurse, a

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[16] del Rio, Mehta, Lyon, & Guarner, *supra* note 12, at 746.

[17] *Id*. at 746–747. *See generally*, NATIONAL LIBRARY OF MEDICINE, *Isolation Precautions*, http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000446.htm (explaining the different types of isolation precautions).

[18] *Id.* (noting that incineration is rarely available in the field and is not usual practice in Africa).

[19] Fauci, *supra* note 7, at 1085.

[20] D. Gatherer, *The 2014 Ebola Virus Disease Outbreak in West Africa*, 95 J. OF GEN. VIROLOGY 1619, 1619 (2014).

[21] *Id*.

[22] K. Sack, S. Fink, P. Belluck, and A. Nossiter, *How Ebola Roared Back*, THE NEW YORK TIMES, December 29, 2014, http://www.nytimes.com/2014/12/30/health/how-ebola-roared-back.html (last visited Feb. 29, 2016) (describing how one-year-old "Emile had taken ill in late December with fever, vomiting and bloody stool"). Many sources describe Emile as a 2-year-old child. *E.g.*, Gatherer, *supra* note 20, at 1621. According to WHO, he was eighteen months old. WHO, EBOLA IN WEST AFRICA: 12 MONTHS ON, January 15, 2015, http://www.who.int/mediacentre/news/notes/2015/ebola-one-year-on/en/.

[23] WHO, *supra* note 22, at n.p. Prior to the onset of symptoms, Emile was seen playing in his backyard near a tree heavily infested with bats. *Id.*

physician, and other healthcare workers died shortly thereafter.[24] In the following week, members of Emile's extended family also fell sick and died.[25]

On January 24, 2014, "the head of the Meliandou health post informed district health officials of five cases of severe diarrhea with a rapidly fatal outcome."[26] This prompted an investigation by a small team of local health officials.[27] Although the investigation was inconclusive, the reported symptoms—including diarrhea, vomiting, and severe dehydration—"appeared similar to those of cholera, one of the area's many endemic infectious diseases."[28] A second, larger investigation also supported the conclusion that the unknown disease was likely cholera.[29]

An infected member of Emile's family carried the Ebola virus to the Guinean capital, Conakry, on February 1, 2014.[30] He died there, four days later, in a hospital.[31] No measures had been taken to protect either the hospital's staff or its other patients, as doctors had no reason to suspect the man was infected with Ebola.[32] As the month of

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[24] *E.g.*, Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p.

[25] WHO, *supra* note 22, at n.p.

[26] *Id.*

[27] *Id.*

[28] *Id.*

[29] *Id*. Cholera is an acute diarrheal infection "that can kill within hours if left untreated." *See generally*, WHO, Cholera Fact Sheet No. 107, http://www.who.int/mediacentre/factsheets/fs107/en/.

[30] WHO, *supra* note 22, at n.p.

[31] *Id.*

[32] *Id*.

February progressed, cases of EVD spread to additional prefectures—Macenta, Baladou, Nzerekore, and Farako—as well as to villages and cities en route to these destinations.[33]

The Ministry of Health of Guinea issued its first alert to the unidentified disease on March 13, 2014.[34] A team sent by the Ministry of Health arrived in Guéckédou the next day.[35] On March 18, a team sent by Médecins sans Frontières (MSF), or Doctors without Borders, arrived.[36] Epidemiologic investigation began, and blood samples were collected and sent to laboratories in France and Germany for virologic analysis.[37] Ebola was identified on March 21.[38] The WHO issued its first communiqué on a new outbreak of EVD on March 23, 2014.[39]

In what has been called "some of the worst luck in epidemiological history,"[40] this Ebola outbreak—the 25th known outbreak of EVD[41]—occurred at the intersection of Liberia, Guinea, and Sierra Leone, three of the world's poorest, least developed countries. An editorial in the prestigious NEW ENGLAND JOURNAL OF MEDICINE concluded that the vast scale of the outbreak was "likely to be a result of the combination of dysfunctional health

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[33] *Id.*

[34] *Id.* ("On that same day, staff at WHO's Regional Office for Africa (AFRO) formally opened an Emergency Management System event for a disease suspected to be Lassa fever.").

[35] Baize, Pannetier, Oestereich, et al, *supra* note 8, at 1418–1419.

[36] *Id*.

[37] *Id*. at 1419.

[38] WHO, *supra* note 22, at n.p.

[39] WHO, *Ebola Virus Disease in Guinea*, March 23, 2014, http://www.who.int/csr/don/2014_03_23_ebola/en/.

[40] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p.

[41] J.J. Farrar and P. Piot, *The Ebola Emergency—Immediate Action, Ongoing Strategy*, 371 NEJM 1545, 1545 (2014).

systems, international indifference, high population mobility, local customs, densely populated capitals, and lack of trust in authorities after years of armed conflict."[42] The editorialists succinctly (and damningly) enumerated the barriers and shortcomings that made the West African Ebola outbreak difficult to control; however, those barriers and shortcomings deserve some further elaboration here.

This is a region where doctors are "rarer than paved roads."[43] Liberia and Sierra Leone have some of the worst physician-patient ratios in West Africa.[44] The initially meager healthcare workforce was further diminished by the "unprecedented" number of healthcare workers infected with the Ebola virus.[45] Nearly 700 healthcare workers were infected by the end of 2014, and more than half of these died.[46] When the outbreak began, hospitals and clinics lacked essentials like running water, soap, and personal protective equipment.[47] Guinea, Sierra Leone, and Liberia were already coping with major health challenges, including malaria and other endemic diseases.[48] Moreover, this was the first

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[42] *Id.*

[43] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p. ("Liberia, for instance, had fewer than 250 physicians for 4 million people").

[44] del Rio, Mehta, Lyon, & Guarner, *supra* note 12, at 746 (explaining that there are "more than 86 000 patients per physician in Liberia and 45 000 patients per physician in Sierra Leone").

[45] WHO, *supra* note 22, at n.p.

[46] *Id.*; *see also*, WHO, *Health Worker Ebola Infections in Guinea, Liberia, and Sierra Leone*, May 21, 2015, http://www.who.int/hrh/documents/21may2015_web_final.pdf (last visited Feb. 29, 2016). There are concerns that the loss of healthcare workers attributable to the 2014 Ebola outbreak will have a staggering effect on non-Ebola mortality even after the countries are declared Ebola-free. *See generally*, David K. Evans, Markus Goldstein, & Anna Popova, *Health-care Worker Mortality and the Legacy of the Ebola Epidemic*, 3 THE LANCET GLOBAL HEALTH e439 (2015).

[47] Fauci, *supra* note 7, at 1085.

[48] *Id*.

major outbreak of Ebola in West Africa, and "the affected countries had weak capacity and structures for epidemic preparedness and response, particularly for viral hemorrhagic fever."[49] Additionally, international health workers had largely pulled out of West Africa in the 1990s, when civil wars devastated Liberia and Sierra Leone.[50] As a result, it took more than three months to diagnose Ebola as the cause of the outbreak; a public health emergency was not declared until five months later; and it was nearly two more months before a humanitarian response was put into place.[51]

A homogenous community with shared socio-cultural roots lives along the borders of Guinea, Liberia, and Sierra Leone,[52] and individuals move easily across the porous national borders.[53] The extensive cross-border movement of people facilitated the rapid spread of Ebola virus across West Africa.[54] Such movement also complicated tracking and follow-up of contacts.[55] Moreover, as the situation improved in one country, patients seeking unoccupied treatment beds were drawn from neighboring countries, a practice

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[49] WHO, *Ebola Virus Disease, West Africa – update*, July 3, 2014, http://www.who.int/csr/don/2014_07_03_ebola/en/; *see also* del Rio, Mehta, Lyon, & Guarner, *supra* note 12, at 746 (explaining that the most useful tests for diagnosing Ebola have not been readily available in the remote areas of Africa where most outbreaks have occurred).

[50] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p.

[51] Farrar & Piot, *supra* note 41, at 1545–1546. The NEW YORK TIMES Editorial Board called the WHO's handling of the Ebola outbreak "anemic" and asserted that the agency's lapses have rightly been blamed on poor leadership in Geneva and in the WHO's regional office in Africa. The Board noted that the office in Africa was "slow to respond, partly because it was staffed by politically appointed people of little competence and partly because it feared that declaring a widespread emergency would tarnish the regulation and international trade of afflicted countries." The Editorial Board, *Reform After the Ebola Debacle*, THE NEW YORK TIMES, February 10, 2015.

[52] WHO, *supra* note 49, at n.p.

[53] WHO, *supra* note 22, at n.p.

[54] WHO, *supra* note 49, at n.p.

[55] *Id.*

which reignited transmission chains.[56] Although roads were unpaved, villagers could ride motorcycles into densely populated cities.[57] In West Africa, cities became "epicenters of intense virus transmission."[58] The spread of EVD into cities further complicated contact tracing.[59]

Additional challenges arose because distrust of government ran high due to decades of conflict.[60] Many West Africans had to be convinced that EVD was real[61] and reacted with indignation to outsiders demanding that they stop providing hands-on care to their sick relatives and friends.[62] Although governments sought to educate the public that Ebola was spread through contact with feces, vomit, and blood and that bodies remained highly contagious even after death, people continued to care for the living[63] and to wash the dead,

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[56] WHO, *supra* note 22, at n.p.

[57] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p.*; see also* D.F. Maron, *Motorcycling to Ebola Treatment Could Spread the Infection*, SCIENTIFIC AMERICAN, September 17, 2014 ("During the journey a weak patient, clinging to the [motorcycle taxi] driver, may expel diarrhea and literally drape herself over the driver even as her bodily fluids permeate the seat. In the process the driver may get infected."); L. Epatko, *WHO: 'Many Thousands of New Cases' of Ebola Expected in Liberia*, PBS Newshour, September 8, 2014 ("In a way, the use of motorcycles is a sign of how convoluted the struggle with Ebola has become. In early September, the [WHO] donated two dozen motorcycles to the Ministry of Health in Guinea, one of the countries hit hardest by the Ebola virus. A week later, WHO said motorbikes used as taxis were one of the ways Ebola was spreading in Liberia.").

[58] WHO, *supra* note 22, at n.p.

[59] Fauci, *supra* note 7, at 1085.

[60] *Id.*

[61] *See, e.g.*, Caelainn Hogan, '*There Is No Such Thing as Ebola*,' THE WASHINGTON POST, July 18, 2014, https://www.washingtonpost.com/news/morning-mix/wp/2014/07/18/there-is-no-such-thing-as-ebola/ (last visited Mar. 4, 2016) ("[A man from a rural part of Sierra Leone] was adamant, like many others in his community, that 'there is no such thing as Ebola.'").

[62] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p.

[63] *See* H. Cooper, *Ebola's Cultural Casualty: Hugs in Hands-On Liberia*, THE NEW YORK TIMES, October 4, 2014, http://www.nytimes.com/2014/10/05/world/africa/ebolas-cultural-casualty-hugs-in-hands-on-liberia.html (describing a mother caring for her 2-year-old daughter who was "feverish, vomiting blood and in pain"); *see also* Norimitsu Onishi, *For a Liberian Family, Ebola Turns Loving Care Into Deadly Risk*, THE NEW YORK TIMES, November 13, 2014, http://www.nytimes.com/2014/11/14/world/africa/in-ebola-outbreak-in-liberia-a-

a step which they "considered essential to a dignified burial and a contended afterlife," in a manner that promoted spread of the virus.[64] These high-risk cultural practices led to extensive exposures to Ebola virus in the community, and facilitated the virus's transmission.[65] Reliance on traditional healers, lack of compliance with advice to seek early medical care, and stigma surrounding Ebola also disrupted control efforts.[66]

Cases of EVD were subsequently confirmed in Senegal, first in a young man who travelled to Dakar, from his home in Guinea, by car, and in Mali, first in a two-year-old from Guinea.[67] Many commentators were quick to note that the unprecedented Ebola epidemic in West Africa occurred "in an age when air travel brings us together like never before."[68] Early in 2014, Dr. Fauci presciently predicted that "global air transit could, and most likely will, allow an infected person to board a plane and unknowingly carry Ebola virus."[69] The

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familys-strength-can-be-its-fatal-flaw.html?_r=0 ("[M]any victims in the region are still being treated within the family, a place of succor – and a font of contagion.").

[64] Sack, Fink, Belluck, & Nossiter, *supra* note 22, at n.p. During previous Ebola outbreaks, adherence to ancestral funeral and burial rites was singled out as fueling large explosions of new cases. WHO, *supra* note 22, at n.p. However, medical anthropologists have described the funeral and burial practices in West Africa as exceptionally high-risk. *Id.* (describing burial practices).

[65] WHO, *supra* note 49, at n.p.

[66] WHO, *supra* note 22, at n.p. *See, e.g.,* United Nations Population Fund, *Ebola Survivors Facing Stigma, Unemployment, Exclusion*, Feb. 3, 2015, http://www.unfpa.org/news/ebola-survivors-facing-stigma-unemployment-exclusion (last visited Mar. 4, 2016) ("Many [survivors in Liberia] say they are encountering hostility, exclusion and unemployment when they return to their communities."); Helene Cooper, *They Helped Erase Ebola in Liberia. Now Liberia Is Erasing Them*, THE NEW YORK TIMES (Dec. 9, 2015), http://www.nytimes.com/2015/12/10/world/africa/they-helped-erase-ebola-in-liberia-now-liberia-is-erasing-them.html (last visited Mar. 4, 2016) ("Still, they [those who helped cremate bodies] are largely shunned by Liberian society.").

[67] WHO, *supra* note 22, at n.p. The first case in Senegal was confirmed on August 29, and the first case in Mali was confirmed on October 23. *Id*.

[68] del Rio, Mehta, Lyon, & Guarner, *supra* note 12, at 747.

[69] Fauci, *supra* note 7, at 1085.

virus flew into Lagos, Nigeria on July 20, 2014[70] and into Dallas, Texas on September 30, 2014.[71] These were the first times that the virus entered a new country via air travel.[72] Both imported and locally acquired cases were eventually reported in the United States[73] and in other countries outside of West Africa.[74]

The majority of Ebola "cases and deaths were reported between August and December 2014, after which time case incidence began to decline as a result of the rapid scale-up of treatment, isolation, and safe burial capacity in" Guinea, Liberia, and Sierra Leone.[75] In January 2016, WHO declared an end to the Ebola outbreak, the deadliest on record.[76] WHO's announcement "mark[ed] the first time since the start of the epidemic . . . that Guinea, Liberia, and Sierra Leone — the three countries that were hardest hit by the virus — had reported zero cases for at least 42 days, or two incubation periods of the

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[70] The virus entered Lagos by way of a symptomatic air traveler, Patrick Sawyer, whose sister, Princess, had just died from Ebola in Liberia. M. Daly, *He Could Have Brought Ebola Here: Minnesota Widow on Her Husband*, The Daily Beast, July 30, 2014, http://www.thedailybeast.com/articles/2014/07/30/minnesota-widow-on-her-husband-he-could-have-brought-ebola-here.html. Sawyer told the hospital staff he had malaria, and as malaria is not transmitted person-to-person, healthcare workers did not take protective precautions. WHO, *supra* note 22, at n.p.

[71] WHO, *supra* note 22, at n.p.

[72] *Id.* On February 19, 2016 it was announced that the U.S. is "no longer conducting enhanced entry screening for Ebola" for travelers coming to the United States. CDC, *2014 Ebola Outbreak in West Africa*, http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/ (last visited Feb. 29, 2016).

[73] CDC, *Cases of Ebola Diagnosed in the United States*, http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html (last visited Apr. 1, 2016).

[74] HEALTH MAPS, *2014 Ebola Outbreaks*, http://www.healthmap.org/ebola/#timeline (last visited Apr. 13, 2015).

[75] WHO, WHO: EBOLA SITUATION REPORT, 6 January 2016, http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016 (last visited Apr. 15, 2016).

[76] Dionne Searcey, Nick Cumming-Bruce, & Clair MacDougall, *Deadliest Ebola Outbreak on Record is Over, W.H.O. Says*, THE NEW YORK TIMES (Jan. 14, 2016), http://www.nytimes.com/2016/01/15/world/africa/ebola-who.html (last visited Apr. 15, 2016).

virus."[77] Although the outbreak has been "stopped,"[78] WHO continues to caution that future flare-ups of EVD are to be expected.[79]

C. The State of Vaccines and Treatments in 2014

At the time the West African Ebola outbreak began no vaccine or medication was proven effective in humans against Ebola. Even today, there are *no* "FDA-approved vaccines or therapeutics available for prevention, postexposure, or treatment for EVD."[80] Treatment consists of supportive care, providing oral rehydration and/or IV fluids with electrolytes, and treating complications.[81] Notably, the standard of care for treatment of hemorrhagic fevers, of which EVD is one, "has not changed appreciably *since the 1950s*."[82]

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[77] *Id.*

[78] WHO, *Latest Ebola Outbreak Over in Liberia; West Africa is at Zero, But New Flare-Ups are Likely to Occur*, http://www.who.int/mediacentre/news/releases/2016/ebola-zero-liberia/en/ (last visited Feb. 26, 2016).

[79] *Id.*

[80] CDC, *Ebola Virus Disease (EVD) Information for Clinicians in U.S. Healthcare Settings*, http://www.cdc.gov/vhf/ebola/healthcare-us/preparing/clinicians.html (last visited Jan. 6, 2016).

[81] WHO, *supra* note 22, at n.p.

[82] del Rio, Mehta, Lyon, & Guarner, *supra* note 12, at 747 (emphasis added) (citing Joseph E. Smadel, *Epidemic Hemorrhagic Fever*, 43 AM. J. OF PUBLIC HEALTH 1327 (1953). Even in the absence of effective treatments, an outbreak can be controlled by taking steps such as isolating patients, placing contacts under fever surveillance, isolating the febrile until a diagnosis is made, and educating the community on minimizing the risks of infection. F. Lamontagne, C, Clément, T. Fletcher, S.T. Jacob, W.A. Fischer, R.A. Fowler, *Doing Today's Work Superbly Well—Treating Ebola with Current Tools*, 371 NEJM 1565, 1566 (2014).

1. A Neglected Disease

Until 2014, fewer than 2,400 cases of Ebola—of which more than 1,500 were fatal—had been reported since 1976, when EVD was first identified.[83] The sheer rarity of Ebola and the unpredictability of outbreaks doubtlessly slowed the development of targeted vaccines and treatments.[84] The fact that Ebola is solely endemic to Africa has likely also played a role. It has been lamented, for example, that "a vaccine would probably exist today if Ebola affected a large number of people in high-income countries, making research and development financially attractive to drug companies."[85] Given that development of drugs and vaccines is both expensive and cumbersome,[86] and that the people who would most benefit from the development of Ebola therapies live in extreme poverty, it is difficult to attract investors.[87] Those affected by Ebola are widely seen as a vulnerable population whose health needs have not been met by the market economy.[88]

While explanations for lags in drug development are typically in the wheelhouse of ethicists, economists, and health policy experts, the satirical news outlet THE ONION

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[83] Tracy Hampton, *Largest-Ever Outbreak of Ebola Virus Disease Thrusts Experimental Therapies, Vaccines into Spotlight*, 312 JAMA 987, 987 (2014); *see also* WHO, EBOLA VIRUS DISEASE, FACT SHEET NO. 103, http://www.who.int/mediacentre/factsheets/fs103/en/ (last visited Apr. 15, 2016).

[84] *Cf.* Emily A. Largent and Steven D. Pearson, *Which Orphans Will Find a Home? The Rule of Rescue in Resource Allocation for Rare Diseases*, 42 HASTINGS CENTER REPORT 27 (2012).

[85] THE LANCET, *Ebola: A Failure of International Collective Action*, 21 August 2014; *see also* Sara Reardon, *Ebola Treatments Caught in Limbo*, 511 NATURE 520 (2014).

[86] Rick Mullin, C*ost to Develop New Pharmaceutical Drug Now Exceeds $2.5B*, SCIENTIFIC AMERICAN, http://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/ (last visited Mar. 1, 2016).

[87] Justine Calma, *Ebola Drug Killed by Congressional Inaction Less than Two Years Before* Outbreak, NOVA (Oct. 14, 2015), http://www.pbs.org/wgbh/nova/next/body/ebola-drug-halted/ (last visited Mar. 1, 2016).

[88] *Cf.* L. Oprea, A. Braunack-Mayer, & C.A. Gericke, *Ethical Issues in Funding Research and Development of Drugs for Neglected Tropical Diseases*, 35 J. Med. Ethics 310 (2009).

published an article titled *Experts: Ebola Vaccine At Least 50 White People Away*.[89] The article states, "[W]aiting more than 50 white people for an effective prevention measure [is] something the world would simply not allow."[90] The thrust of the article is that if white people, rather than black people, were the primary victims of the Ebola virus, there would already be a vaccine. Race was a lens through which some viewed and critiqued the outbreak and the subsequent response, though the factors were complex.

Although EVD is not on WHO's list of neglected tropical diseases (NTDs), "a diverse group of [17] communicable diseases that prevail in tropical and sub-tropical conditions . . . [and] mainly affect populations living in poverty,"[91] comparisons have been drawn between EVD and the "classic" NTDs.[92] Between 1975 and 2000, "only 10% of global research and development resources were allocated for neglected diseases"[93] despite their pernicious impact on the "bottom billion," those individuals living in the world's most impoverished conditions.[94] Almost everyone in the bottom billion has at least one NTD, and the NTDs serve to reinforce their poverty.[95] While the overall burden of disease due to

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[89] *Experts: Ebola Vaccine At Least 50 White People Away*, THE ONION (Jul. 30, 2014) http://www.theonion.com/article/experts-ebola-vaccine-at-least-50-white-people-awa-36580 (last visited Apr. 7, 2016).

[90] *Id.*

[91] WHO, *Neglected Tropical Diseases*, http://www.who.int/neglected_diseases/diseases/en/ (last visited Feb. 29, 2016).

[92] *E.g.*, Adam MacNeil & Pierre E. Rollin, *Ebola and Marburg Hemorrhagic Fevers: Neglected Tropical Diseases?*, 6 PLoS NEGL. TROP. DIS. e1546 (2012).

[93] Ripudaman Bains, *A Ticking Time Bomb? Ebola and The Neglected Tropical Diseases*, BioMed Central (Nov. 27, 2014), http://blogs.biomedcentral.com/on-biology/2014/11/27/a-ticking-time-bomb-ebola-and-the-neglected-tropical-diseases/ (last visited Mar. 5, 2016).

[94] MacNeil & Rollin, *supra* note 92, at n.p.

[95] Peter J. Jotez, Alan Fenwick, Lorenzo Savioli, & David H. Molyneux, *Rescuing the Bottom Billion Through Control of Neglected Tropical Diseases*, 373 LANCET 1570, 1570 (2009).

EVD is dwarfed in comparison to the classic NTDs, when "examined from a bottom billion viewpoint, there are multiple factors supporting the notion that [the] disease, and particularly outbreaks, are components of impoverished conditions."[96]

When existing or emerging viruses that cause diseases like EVD are neglected, that neglect exacerbates global health inequalities and directly implicates questions of distributive justice.[97] Thus, there is a moral and ethical dimension to the 2014 EVD outbreak—and to the lack of vaccines and therapies that, in part, allowed the virus to spread. Complicating this analysis, however, is the fact that, due to concerns over the potential use of Ebola as a biological weapon,[98] the U.S. government and others have provided substantial funding for Ebola research.[99] Since 2003, for instance, the Defense Threat Reduction Agency, an agency within the U.S. Department of Defense that supports efforts to combat weapons of mass destruction,[100] "has invested more than $300 million to

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[96] MacNeil & Rollin, *supra* note 92, at n.p.

[97] *Cf.* C.A. Gericke, A. Riesberg, & R. Busse, *Ethical Issues in Funding Orphan Drug Research and Development*, 31 J. MED. ETHICS 164 (2005); Oprea, Braunack-Mayer, & Gericje, *supra* note 88.

[98] *See generally*, Calma, *supra* note 87, at n.p. ("Ebola has been classified as a Category A bioterrorism threat by the U.S. Centers for Disease Control and Prevention (CDC) since at least 2004."); Dina Fine Maron, *Weaponized Ebola: Is It Really a Bioterror Threat?*, SCIENTIFIC AMERICAN (Sept. 25, 2014), http://www.scientificamerican.com/article/weaponized-ebola-is-it-really-a-bioterror-threat/ (last visited Feb. 29, 2016).

[99] *See, e.g.*, Rick Noack, *Why Ebola Worries the Defense Department*, THE WASHINGTON POST (Aug. 5, 2015), https://www.washingtonpost.com/news/worldviews/wp/2014/08/05/why-ebola-worries-defense-department/ (last visited Feb. 29, 2016).

[100] Defense Threat Reduction Agency, *Who We Are*, http://www.dtra.mil/About/WhoWeAre.aspx (last visited Feb. 29, 2016).

develop medical countermeasures against hemorrhagic fever viruses" including Ebola.[101] In 2013, NIAID spent more than $42 million on Ebola research.[102]

In fact, some suggest that "disproportionate resources" have been deployed for Ebola research and control as compared to other neglected diseases.[103] As a result of this investment, progress was made in understanding the Ebola virus and in developing potential therapies.[104] Nevertheless, writing on the eve of the 2014 outbreak, two clinicians from the U.S. Centers for Disease Control and Prevention (CDC) observed that "from the perspective of those most at risk of [EVD], . . . progress has not been experienced."[105]

2. Experimental Interventions, Repurposing, and Off-Label Use

When the 2014 EVD outbreak began, several Ebola-specific drugs and vaccines were already under development.[106] The most promising of these—most prominently, perhaps, ZMapp, a combination of three different monoclonal antibodies, developed by Mapp

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[101] Cheryl Pellerin, *DTRA Medical Countermeasures Help Western African Ebola Crisis*, http://www.defense.gov/News-Article-View/Article/603806 (last visited Feb. 29, 2016) ("[T]hose efforts are paying off today in potential new ways to fight Ebola virus disease.").

[102] Zoë Schlanger & Elijah Wolfson, *The U.S. Is Sitting On Promising Ebola Vaccines*, NEWSWEEK (Aug. 4, 2014), http://www.newsweek.com/2014/08/15/us-sitting-promising-ebola-vaccines-262870.html (last visited Mar. 7, 2016).

[103] David H. Molyneux, *"Neglected" Diseases But Unrecognised Successes—Challenges and Opportunities for Infectious Diseases Control*, 364 THE LANCET 380, 380 (2004).

[104] MacNeil & Rollin, *supra* note 92, at e1546.

[105] *Id.*

[106] *Id*.

Biopharmaceutical Inc.[107]—"all [had] roots in programs run by the Department of Defense."[108] Yet, Dr. Luciana Borio of FDA noted at the time that

> [t]he experimental vaccines and treatments in development are in the earliest investigational stages and have not been fully tested for safety or efficacy. Only small amounts of some experimental products have been manufactured for testing, which means few courses, if any, are available.[109]

In addition to these investigational, Ebola-specific vaccines and treatments, there was also interest in repurposing FDA-approved drugs—that is, drugs previously approved by the FDA for other indications—as treatments for EVD.[110] Repurposing is the process where a drug that is patented and FDA-approved for treating one disease is further developed for the purpose of treating another disease.[111] Drugs could also be used "off-label." Off-label use is the prescribing of a drug or biologic agent for a treatment regimen not specified in the FDA-approved labeling or package insert.[112]

> The legislative history of the Federal Food, Drug, and Cosmetic [(FD&C)] Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Once a drug is approved for marketing, FDA does not generally regulate

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[107] CDC, *Questions and Answers on Experimental Treatments and Vaccines for Ebola*, August 29, 2014, http://www.cdc.gov/vhf/ebola/outbreaks/guinea/qa-experimental-treatments.html (last visited Mar. 8, 2016).

[108] *See generally*, Calma, *supra* note 87, at n.p.

[109] Luciana Borio, *FDA Works to Mitigate the West Africa Ebola Outbreak* (Aug. 22, 2014), http://blogs.fda.gov/fdavoice/index.php/tag/emergency-investigational-new-drug-eind/#sthash.DU5oGuVB.dpuf (last accessed Jan. 8, 2015).

[110] Sean Ekins & Megan Coffee, *FDA Approved Drugs as Potential Ebola Treatments*, F1000 RESEARCH (2015), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358410/pdf/f1000research-4-6664.pdf.

[111] Daniel S. Sem, *Repurposing - Finding New Uses for Old (and Patented) Drugs: Bridging the "Valley of Death," to Translate Academic Research into New Medicines*, 18 Marquette Intellectual Property L. Rev. 143, 143–144 (2014).

[112] *See generally*, Emily A. Largent, Franklin G. Miller, and Steven D. Pearson, *Going Off-label Without Venturing Off Course*, 169 ARCHIVES OF INTERNAL MEDICINE 1745 (2009).

> how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling.[113]

While concerns may arise when existing drugs are repurposed or prescribed off-label in a public health emergency, given the lack of alternatives, many felt repurposing and off-label prescribing were worth trying.[114]

II. Calls for the Use of Experimental Interventions in the 2014 Outbreak

As established above, at the onset of the 2014 EVD outbreak—the deadliest on record—the standard of care for hemorrhagic fevers, including EVD, had not progressed appreciably beyond supportive care since the 1950s. Due, however, to investments made by the U.S. Department of Defense and others, several candidate vaccines and treatments were in the works. Given the relative dearth of treatment options and a case fatality rate reported to be between 53 and 60%,[115] calls were made for the use of experimental interventions in the field.[116] In late August 2014, for instance, a panel convened by WHO

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[113] William B. Schultz, *Statement Before the Senate Committee on Labor and Human Resources* (Feb. 22, 1996), http://www.fda.gov/newsevents/testimony/ucm115098.htm (last viewed Feb. 29, 2016).

[114] *E.g.*, *Fast-tracking Treatments: The Hunt for Ebola Medicines is Being Accelerated*, THE ECONOMIST, http://www.economist.com/news/science-and-technology/21616888-hunt-ebola-medicines-being-accelerated-fast-tracking-treatments (last viewed Feb. 29, 2016); *see also*, P.B. Madrid, S. Chopra, I.D. Manager, et. al, *A Systematic Screen of FDA-Approved Drugs for Inhibitors of Biological Threat Agents*, 8 PLOS ONE e60579 (2013) (discussing advantages of off-label use, such as the known safety and pharmacokinetic profiles, as well as existing manufacturing and distribution networks).

[115] WHO Ebola Response Team, *supra* note 2, at 1.

[116] *See, e.g.,* Hampton, *supra* note 83, at 987–989; Thomas R. Frieden, Inger Damon, Beth P. Bell, Thomas Kenyon, and Stuart Nichol, *Ebola 2014—New Challenges, New Global Response and Responsibility*, 371 NEJM 1177 (2014); Erika Check Hayden & Sara Reardon, *Should Experimental Drugs Be Used in the Ebola Outbreak?*, NATURE (Aug. 12, 2014), http://www.nature.com/news/should-experimental-drugs-be-used-in-the-ebola-outbreak-1.15698 (last visited Mar. 1, 2016).

concluded that an ethical imperative existed "to offer the available experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing [Ebola]" as long as ethical criteria guided the provision of such interventions.[117]

Using experimental interventions—particularly in the midst of an outbreak difficult to bring under control for the host of social, political, and economic reasons discussed in Section I, above—poses practical and ethical challenges.[118] A challenge of particular relevance to FDA—and therefore a focus of this article—is that of gathering high-quality evidence to prove that a novel drug or vaccine is both safe and effective when used in humans. Before a vaccine or drug can be approved by FDA for marketing, it must be rigorously evaluated for quality, safety, and efficacy.[119]

Given the history of investment by the Department of Defense in Ebola-related interventions, specifically those that were thought in 2014 to be most promising, and the likely role of the U.S. government as an eventual buyer of these interventions, calls to use

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[117] WHO, ETHICAL CONSIDERATIONS FOR USE OF UNREGISTERED INTERVENTIONS FOR EBOLA VIRAL DISEASE: REPORT OF AN ADVISORY PANEL TO WHO.

[118] *See, e.g.*, Annette Rid & Ezekiel J. Emanuel, *Ethical Considerations of Experimental Interventions in the Ebola Outbreak*, 384 THE LANCET 1896 (2014); Carl H. Coleman, *Control Groups on Trial: The Ethics of Testing Experimental Ebola Treatments*, 7 J. BIOSECURITY, BIOSAFETY AND BIODEFENSE LAW (2016, Forthcoming) (discussing the ethics of randomized controlled trials in an epidemic); see *also*, Emily A. Largent, *Recently Proposed Changes to Legal and Ethical Guidelines Governing Human Subjects Research*, JOURNAL OF LAW & BIOSCIENCES, doi:10.1093/jlb/lsw001 (2016) (discussing proposed changes to the Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines for Biomedical Research, particularly Proposed Guideline 20, Research in Disaster Situations).

[119] Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAGAZINE (Jan.-Feb. 2006), http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/ (last viewed Feb. 29, 2016). Between the passage of the Federal Food, Drug, and Cosmetic Act in 1938 (Public Law 75-717) and the adoption of the 1962 Kefauver-Harris Drug Amendments (Public Law 87-781), drug manufacturers were required to show only that their drugs were safe. The 1962 amendments included a provision requiring manufacturers to establish a drug's effectiveness by "substantial evidence."

experimental interventions in the field directly implicated FDA. Although Ebola is not endemic in the United States, if an intervention will be stockpiled and/or used by the American military, as Ebola drugs and vaccines likely would be, "all critical functions in the development and acquisition . . . lead to and through FDA."[120]

Additionally, although national regulatory authority (NRA) officials in any Ebola-affected country are ultimately responsible for determining whether a medical countermeasure for Ebola should be approved for use within the nation's borders,

> [a]pproval from a stringent regulatory authority such as the US [FDA] . . . can expedite another country's NRA review, given that such approval signifies to international medical and regulatory communities that the data have been thoroughly examined and . . . meet[] performance and manufacturing standards.[121]

Drug and vaccine manufacturers therefore had several clear incentives to work with FDA in the West African outbreak despite FDA's geographic remove.

The particulars of FDA's response to the 2014 outbreak are the focus of Sections III and IV. In this section, I provide general background on the distinction between clinical research and clinical care and then advance an argument, which is both practically and normatively grounded, that, even in the midst of an Ebola outbreak, it is essential to deliver innovative therapies in the course of randomized controlled research rather than in the

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[120] Richard A. Rettig & Jennifer Brower with Orlie Yaniv, THE ACQUISITION OF DRUGS AND BIOLOGICS FOR CHEMICAL AND BIOLOGICAL WARFARE DEFENSE: DEPARTMENT OF DEFENSE INTERACTIONS WITH THE FOOD AND DRUG ADMINISTRATION, RAND at 2 (2003) ("At the heart of the DoD [Department of Defense] acquisition process for drugs and biologics, then, are FDA requirements that must be met . . . This reality creates for DoD a dependence on FDA, another government agency, in meeting its national security requirements for CBW [chemical and biological warfare] defense.").

[121] WELLCOME TRUST & CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY (CIDRAP) AT UNIVERSITY OF MINNESOTA, PLOTTING THE COURSE OF EBOLA VACCINES: CHALLENGES AND UNANSWERED QUESTIONS (2016), http://www.cidrap.umn.edu/sites/default/files/public/downloads/ebola_team_b_report_2-033116-final.pdf (last visited Apr. 12, 2016).

course of clinical care if at all possible. Understanding why robust research is essential helps to position my evaluation of FDA's response to the 2014 outbreak, as well as my recommendations for future outbreaks.

A. The Research-Care Distinction

Gathering evidence that a vaccine or drug is safe and effective for use in humans requires the systematic conduct of human subjects research, research in which human beings ("as opposed to animals, atoms, or asteroids"[122]) are the subjects of study. Clinical research, a type of human subjects research, explores new ways to prevent, detect, or treat illness in order to improve human health and well being.[123]

Clinical research has long been distinguished from clinical care.[124] Clinical care refers to interventions "designed solely to enhance the well-being of an individual patient . . . and that have a reasonable expectation of success. The purpose of medical . . . practice is to provide diagnosis, preventive treatment, or therapy to particular individuals."[125] By contrast, research is "designed to test an hypothesis, permit conclusions to be drawn, and

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[122] David Wendler, *The Ethics of Clinical Research*, THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Fall 2012 Edition), Edward N. Zalta (ed.), http://plato.stanford.edu/archives/fall2012/entries/clinical-research/ (last visited Jan. 4, 2016).

[123] *Id.; see generally,* NIH*, Clinical Research Trials and You: The Basics*, http://www.nih.gov/health-information/nih-clinical-research-trials-you/basics (last visited Mar. 1, 2016).

[124] There have been influential calls to integrate research and care. The integration of research and care within so-called "learning healthcare systems" holds the potential to advance socially valuable research, to yield health benefits for current and future patients, and to improve the quality of care while lowering. INSTITUTE OF MEDICINE (IOM), BEST CARE AT LOWER COST: THE PATH TO CONTINUOUSLY LEARNING HEALTH CARE IN AMERICA (2012). Yet, even as research and care are routinely and systematically integrated, the normative importance of the research-care distinction remains. Emily A. Largent, Steven Joffe, and Franklin G. Miller, *Can Research and Care Be Ethically Integrated?*, 41 No. 4 HASTINGS CENTER REPORT 37 (2011).

[125] THE NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979).

thereby develop or contribute to generalizable knowledge . . . . Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective."[126]

Central to the distinction between research and care is the idea that the purpose of clinical research is fundamentally different from that of clinical medicine: whereas medical care focuses on providing optimal care to individual patients, clinical research is primarily concerned with producing knowledge for the benefit of future patients.[127] Other characteristics of research include use of distinctive methods—such as randomization, placebo controls, and blinding—that sacrifice personalization of care in favor of scientific validity and the inclusion of procedures that hold no prospect of medical benefit for the research participant but which are justified in light of their scientific value.[128]

One consequence of the research-care distinction is that research ethics and medical ethics have long been considered distinct sets of normative commitments.[129] Clinical research and clinical care are also regulated differently. Human subjects research is governed by "a series of international codes, national legislation, and agency regulations."[130] FDA, for instance, requires "adherence to the principles of good clinical

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[126] *Id.*; *see also*, 45 CFR § 46.102(d) (2005) (Research is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.").

[127] Largent, Joffe, & Miller, *supra* note 124, at 37.

[128] *Id.* at 37–38.

[129] Emily A. Largent, Steven Joffe, & Franklin G. Miller, *A Prescription for Ethical Learning*, 43 No. 1 HASTINGS CENTER REPORT S28 (2013).

[130] Erin D. Williams, CONGRESSIONAL RESEARCH SERVICE, *Federal Protection for Human Research Subjects: An Analysis of the Common Rule and Its Interactions with FDA Regulations and the HIPAA Privacy Rule*, CRS-12 (2005).

practices (GCPs), including adequate human subject protection,"[131] regardless of the funding source, in studies used to support an application to FDA for research or marketing permits for products regulated by FDA. The International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines—also known as ICH GCP (E6)—are "an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects."[132]

FDA does not, by contrast, regulate the practice of medicine. Rather, longstanding Congressional and FDA policies respect the regulatory role of states.[133] The FD&C Act explicitly states, "[N]othing . . . shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship."[134] This has been interpreted to mean that

> [i]f a physician determines that the use of a device is appropriate for their patient, as long as they're not studying the safety and effectiveness of that device, they may use the device under practice of medicine. Under practice of medicine, the physician should be well informed about the product, and use firm scientific rationale and sound medical evidence to determine whether they should use the device. [135]

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[131] FDA, *Clinical Trials and Human Subject Protection*, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ (last visited Mar. 1, 2016).

[132] HHS, *Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance*, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf. This guidance provides "a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions." *Id.*

[133] Barbara J. Evans, *The Limits of FDA's Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing*, 70 FOOD AND DRUG LAW J. 259, 260 (2015).

[134] 21 U.S.C., Chapter 9, Subchapter X, § 396 (2011).

[135] Soma Kalb, IDE Basics - Transcript, http://www.fda.gov/Training/CDRHLearn/ucm426001.htm (last visited Apr. 7, 2016).

While FDA advises physicians to use "firm scientific rationale and sound medical evidence"[136] to guide their care, including off-label use, "physicians failing to do so would not be answerable to FDA but rather to their state medical practice licensing boards and to plaintiffs in state medical malpractice suits."[137]

The distinction between research and care is of fundamental importance because, once calls were made for the use of experimental interventions in the midst of the 2014 EVD epidemic, I will argue that the need for research was unavoidable. Because research and care are distinct, calls for use of experimental interventions also entailed adherence to distinct ethical and regulatory commitments that became a field for contestation.

B. The Potential Benefits of Research to Current Patient-Participants

Participation in research may or may not offer potential benefits to individual research participants.[138] Offering such benefits is *not* a criterion of ethically acceptable research.[139] In practice, institutional review boards (IRBs), the administrative bodies "established to protect the rights and welfare of human research subjects recruited to participate in research activities,"[140] are required to determine that the risks to individual

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[136] *Id.*

[137] Evans, *supra* note 133, at 265.

[138] For a helpful taxonomy of benefits, *see*, Nancy M.P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 JL MED. & ETHICS 332 (2000).

[139] *See generally*, Ezekiel J. Emanuel, David Wendler, & Christine Grady, *What Makes Clinical Research Ethical?*, 283 JAMA 2701 (2000); *see also*, Ezekiel J. Emanuel, David Wendler, Jack Killen, & Christine Grady, *What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research*, 189 J. INFECT. DIS. 930 (2004).

[140] H.H.S. DEP'T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993).

participants have been minimized and that any residual risks are offset or outweighed by *either* the prospect of individual benefit *or* the social value of the knowledge to be gained. Thus, if the social value is sufficiently high (and all clinical research must have social value to be ethical), research may be IRB-approved even if it offers no potential benefit to research participants.[141]

A prevailing though contested ethical perspective on clinical trials does, however, hold that "clinical equipoise" is necessary for research to be ethically acceptable.[142] Clinical equipoise exists when the medical profession as a whole has not yet reached consensus that one arm of a clinical trial—whether the control or the experimental intervention—offers a therapeutic benefit over the other arm(s).[143] Accordingly, if there is genuine uncertainty that any of the arms is superior, it is ethical for the trial to proceed; individuals cannot, however, ethically be assigned to an arm that is, *ex ante*, known to be worse for them than the others. One implication of this position is that it rules out a placebo-controlled trial whenever a proven-effective treatment exists for a disorder.[144] Critically, "ensuring that equipoise exists is *not* the same as establishing a reasonable chance of benefit."[145]

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[141] In such cases, participation is reasonable, and research participants may be altruistically motivated.

[142] E.g., Paul B. Miller & Charles Weijer, *rehabilitating Equipoise,* 13 KENNEDY INSTITUTE OF ETHICS JOURNAL 93 (2003); *but see*, Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception and the Ethics of Clinical Trials*, 33 HASTINGS CENTER REPORT 19 (2003) (arguing this perspective is flawed because it confuses the ethics of research and of care).

[143] Miller & Brody, *supra* note 142, at 19.

[144] *Id.* at 20 (pointing out the practical and "theoretical incoherence" that IRBs routinely approve placebo-controlled trials).

[145] King, *supra* note 138, at 337 (emphasis added).

Significantly, clinical research *can* provide care for an individual that is good, or even optimal, depending on the alternatives available to the patient as well as on the design of the trial.[146] Nevertheless, it is important to appreciate that some aspects of research participation may not be in an individual's best interest due to the loss of personalization and the inclusion of research-related procedures. For instance, a study protocol may include a research blood draw (e.g., to test the level of drug in an individual's bloodstream) that offers no potential for personal benefit (e.g., treatment wouldn't change on the basis of that blood level; it is simply for researchers to develop an idea of how quickly the drug is metabolized). While a research blood draw is relatively low risk, one could imagine progressively riskier procedures that offer no prospect of personal medical benefit but which are important for the scientific validity of a study. Such procedures, while justified, illustrate the potential tension between patients' individual interests and the aim of research to promote the greater good.

C. The Benefits of Research for Future Patients

Determining whether experimental interventions to prevent or treat EVD—or drugs repurposed or used off-label for EVD—are safe and effective for use in humans can only be accomplished by testing them in people exposed to or infected with the Ebola virus.[147] It would be unethical intentionally to expose healthy research participants to the highly

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[146] Largent, Joffe, & Miller, *supra* note 124, at 38.

[147] Daniel G. Bausch, A.G. Sprecher, Benjamin Jeffs, and Paul Boumandouki, *Treatment of Marburg and Ebola Hemorrhagic Fevers: A Strategy for Testing New Drugs and Vaccines Under Outbreak Conditions*, 78 ANTIVIRAL RESEARCH 150 (2008).

lethal Ebola virus. Therefore, research conducted during outbreaks of EVD is likely to be the primary, if not sole, means of establishing the safety and efficacy of novel interventions. That is, it will be essential to systematically conduct human subjects research in the midst of an Ebola outbreak to secure the body of socially valuable generalizable knowledge needed to benefit those affected by future Ebola outbreaks.

There can, however, be discomfort with conducting clinical research—which, as discussed above, entails different normative commitments than clinical care—in a public health emergency laden with human suffering. Assuming that the status quo (i.e., treatment consisting of supportive care) is not acceptable, an alternative to robust research would be compassionate use, the use of an experimental intervention outside of a clinical trial. In the 2014 Ebola outbreak, some advocated for compassionate use. They maintained that compassionate use was more desirable than rigorous data collection because compassionate use offered "hope for survival despite the fact that the efficacy and adverse effects of the [experimental] drug are unknown."[148] Although compassionate use is theoretically compatible with learning about a drug's safety and efficacy, without well-designed research, it would be difficult to establish the evidence base needed to move the standard of care appreciably beyond where it currently stands going forward.[149]

Thus, a compassion-knowledge trade-off arises. The tradeoff can affect both the current patient—who receives a dose of hope from what is at bottom an unproven intervention—and future Ebola patients—who, going forward, will not benefit from a

[148] Morenike Folayan, Brandon Brown, Aminu Yakubu, Kristin Peterson, & Bridget Haire, *Compassionate Use of the Experimental Drugs in the Ebola Outbreak*, 384 LANCET 1843, 1843 (2014).

[149] Steven Joffe, *Evaluating Novel Therapies During the Ebola Epidemic*, 312 JAMA 1299, 1299 (2014).

largely absent body of generalizable knowledge. The tradeoff can also adversely affect third-parties if compassionate use consumes scarce healthcare resources for uncertain clinical benefits.[150] Emphasis needs to be placed on research to validate the safety and efficacy of experimental interventions because *outcomes for patients collectively are optimized when the practice of medicine is based on current knowledge*.

Of course, there is understandable reluctance to deny anyone presenting with a life-threatening condition like EVD access to a potentially beneficial intervention, to hope. This reluctance is, however, a misguided moral impulse and should not guide policy. The dilemma posed by compassionate use can be analogized to difficulties related to how scarce resources should be allocated between identified and statistical lives. The preference for identifiable lives—individuals currently known to us—over statistical lives—individuals who are as yet unknown or possibly not yet in existence—has been criticized as mistaken by many bioethicists.[151] One argument made in favor of saving identifiable lives, the "symbolic value argument," is that by rescuing identifiable lives, a society demonstrates the value it places on human life, thereby promoting social utility.[152] Yet, "[i]t is unclear why showing respect for *identified* lives better captures this symbolic value of life; indeed, one might think it is statistical lives that captures the notion that all lives are equal and of the same value."[153] The implication of this argument is *not* that

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[150] Annette Rid & Ezekiel J. Emanuel, *Compassionate use of experimental drugs in the Ebola outbreak – Authors' reply,* 384 LANCET 1844, 1844 (2014).

[151] I. Glenn Cohen, *Rationing Legal Services*, 5 J. OF LEGAL ANALYSIS 221, 252 (2013) (listing ethicists who have taken this position).

[152] Largent & Pearson, *supra* note 84, at 30.

[153] Cohen, *supra* note 151, at 252.

identifiable lives do not matter. The implication is that they do not deserve any "preference over the equivalent number of statistical lives."[154] Gains for future patients should not be sacrificed in order to offer a benefit as ephemeral as hope to current patients—particularly when hope is conditioned on receipt of an admittedly unproven intervention. In such circumstances, clinical research rather than compassionate use is the appropriate response.

Rigorous research was ethically appropriate—whether or not one recognizes a role within research ethics for clinical equipoise—because the 2014 Ebola outbreak was characterized by genuine uncertainty. Moreover, research was necessary because the outbreak was likely the sole opportunity, at least until the next outbreak, ethically to conduct research and, hopefully as a result, to have approved vaccines and treatments available in future Ebola epidemics. Even if one accepted, however, that it was both ethically acceptable and imperative to conduct research in the midst of an EVD epidemic, open questions remained about what *kind* of research should be conducted—that is, how the research should be designed and executed. That is the focus of the next sub-section.

[154] *Id.* at 254.

D. An Argument for Randomized Placebo-Controlled Trials

Studies conducted in the midst of a public health emergency "raise difficult ethical, scientific, and practical questions about how best to design and conduct research."[155] One such question is whether it is ethically acceptable to conduct a randomized placebo-controlled trial.[156] This question was highly divisive in the 2014 Ebola outbreak.[157] While some felt that randomized placebo-controlled trials were the optimal means of efficiently identifying safe and effective interventions for EVD, others argued for providing access to potentially beneficial experimental interventions as widely as possible and, therefore, advocated for use of alternative trial designs that did not incorporate randomization to placebo controls.

The debate surrounding randomized placebo-controlled trials had two primary strains. On the one hand, there were questions about whether alternative trial designs were sufficiently methodologically rigorous to yield valid results; on the other, there were questions about whether it was ethical in the context of the 2014 EVD outbreak to randomize individuals to a placebo and deny them the opportunity to benefit from an experimental intervention. I consider each of these in turn and argue that those in favor of randomized placebo-controlled trials held the superior position.

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[155] PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES (PRESIDENTIAL COMMISSION), ETHICS AND EBOLA: PUBLIC HEALTH PLANNING AND RESPONSE, at 33 (2015).

[156] *Id.*

[157] *E.g.*, Joffe, *supra* note 149, at 1300 ("Investigators should instead move directly to randomized trials that compare best supportive care plus an experimental agent with best supportive care alone."); Jon Cohen & Kai Kupferschmidt, *Ebola Vaccine Trials Raise Ethical Issues*, 346 SCIENCE 289, 289 (2014) ("At a consultation held by the World Health Organization (WHO) on 29 to 30 September, . . . there was unexpectedly broad support for the RCT design"); *but see*, Coleman, *supra* note 118, at __ (identifying groups who refused to participate in placebo-controlled trials).

1. Validity of Results

Randomized controlled trials (RCTs) are the gold standard means of assessing whether a potential treatment or vaccine is efficacious. In the preapproval stage at FDA, "RCTs are regarded as fulfilling the statutory requirement of 'adequate and well-controlled' studies to support a marketing claim."[158] Randomization ensures that individuals who receive the experimental intervention do not systematically differ from the control group along observable or unobservable dimensions.[159] This allows valid (i.e., causal) inferences to be drawn about the safety and efficacy of the novel intervention.[160]

A central fear of those opposed to alternative trial designs was that such designs might lack validity and yield biased conclusions. While conceding that "[u]ncontrolled trials can give accurate answers when certain stringent conditions are met, including preliminary evidence of large effect sizes and the availability of data from historical cohorts

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[158] COMMITTEE ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, BOARD ON POPULATION HEALTH AND PUBLIC HEALTH PRACTICE, INSTITUTE OF MEDICINE, *Evidence and Decision-Making*, in ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS (2012) (noting that although "observational studies are a major source of evidence related to drug safety and are playing an increasing role in FDA's oversight of drug safety[, s]uch designs play a relatively minor role in establishing drug safety in the preapproval stage.").

Controversially, the proposed 21st Century Cures Act could change this. Jerry Avorn & Aaron S. Kesselheim, *The 21st Century Cures Act — Will It Take Us Back in Time?* 372 NEJM 2473 (2015) ("[A]s introduced, the 21st Century Cures Act instructs the FDA to consider nontraditional study designs and methods of data analysis to further speed approvals. Adaptive trial designs and the use of Bayesian methods hold promise in some kinds of evaluations, particularly in oncology. However, more problematic proposals include encouraging the use of "shorter or smaller clinical trials" for devices and the request that the FDA develop criteria for relying on "evidence from clinical experience," including "observational studies, registries, and therapeutic use" instead of randomized, controlled trials for approving new uses for existing drugs. Although such data can provide important information about drug utilization and safety once a medication is in use, there is considerable evidence that these approaches are not as rigorous or valid as randomized trials in assessing efficacy.").

[159] Joffe, *supra* note 149, at 1300.

[160] *Id.*

that permit valid comparisons,"[161] they argued that those opposing RCTs had failed to demonstrate those conditions could be met in the West African epidemic.[162]

It is ethically concerning if research participants are exposed to research-related risks and burdens that cannot be justified because a study is not scientifically valid.[163] Moreover, a real concern was that misleading results from an uncontrolled study could have negative ramifications for many stakeholders in a high-stakes situation.

> Mistakenly determining a benefit or missing a potential harm can directly hurt research participants as well as individuals who use the intervention if implemented, and can impose substantial economic costs on communities and societies [by misdirecting scarce healthcare resources]. In contrast, failing to detect a modest but meaningful level of clinical effectiveness might deprive those in need of an intervention that can reduce suffering or improve chances of survival.[164]

Proponents of RCTs argued that a randomized placebo-controlled trial would increase confidence in the accuracy of research findings.

As mentioned above, there is understandable reluctance to deny anyone with a life-threatening condition access to a promising experimental intervention, for example, by screening them out of a clinical trial via inclusion and exclusion criteria or by randomizing them to a placebo-control arm. However, if only RCTs can provide reliable information about safety and efficacy, then alternative trial designs unacceptably favor current patients at the expense of future patients—a position which is not ethically tenable. A moral impulse to offer a potential benefit to current patients cannot overcome concerns about the

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[161] *Id.* (internal citations omitted).

[162] *Id.*

[163] Emanuel, Wendler, & Grady, *supra* note 139, at 2704.

[164] PRESIDENTIAL COMMISSION, *supra* note 155, at 35.

validity of research results.

A practical concern that informed the debate about validity of results was that, as mentioned above, only small amounts of experimental interventions had been manufactured at the time of the 2014 outbreak. This meant that few courses were available for use in research. This point was made by those opposed to RCTs. Of course, if insufficient amounts were available to allow for the conduct of scientifically valid studies, then RCTs should not be performed.[165] To do so would unacceptably expose research participants to research-related risks that could not be justified.[166] Yet, the possibility of misleading results due to too small sample sizes is also an argument against conducting non-randomized or uncontrolled studies because the requirements of social value and scientific validity are universal.[167] Therefore, the argument from small quantities risked proving too much.

Even accepting that it is possible for alternative trial designs to yield valid results that constitute a sufficiently robust basis for both clinical practice and health policy, it is necessary to concede that in any particular circumstances, methodologists must determine that alternative trial designs are appropriate. In the 2014 outbreak, the position in favor of alternative designs did not secure sufficient consensus among methodologists to justify moving away from the gold standard of RCTs. Therefore, it was essential to answer the outstanding normative question: whether research participants can ethically be randomized to a placebo control.

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[165] Steven Joffe, *Ethical Testing of Experimental Ebola Treatments—Letter to the Editor*, 313 JAMA 422, 422 (2015).

[166] Emanuel, Wendler, & Grady, *supra* note 139, at 2703–2704.

[167] Joffe, *supra* note 165, at 422.

2. Ethical Acceptability of Placebo Use

A primary objection made to the conduct of RCTs in the 2014 outbreak was that it was unethical to randomize individuals to a control arm—that is, not to give them access to a promising experimental intervention—given the high case fatality rate of Ebola.[168] For example, a prominent editorial in the LANCET asserted, "When conventional care means such a high probability of death, it is problematic to insist on randomising patients to [conventional (i.e., supportive) care] when the intervention arm holds out at least the possibility of benefit."[169] I will argue, however, that proponents of this position are mistaken. Use of placebo controls would be ethical.

First, as the editorial acknowledged, in an RCT evaluating an experimental intervention for EVD, research participants would likely be randomized to receive either (1) the experimental intervention in conjunction with the necessary supportive care or (2) supportive care only or, possibly, supportive care plus a placebo.[170] It is essential to underscore that in such trials, receiving a placebo or being assigned to the control arm is not equivalent to *no care*. Supportive care was not available to many people in West Africa

[168] *E.g.*, Clement Adebamowo, Oumou Bah-Sow, Fred Binka, et al., *Randomised Controlled Trials for Ebola: Practical and Ethical Issues*, 384 LANCET 1423, 1423 (2014); Morenike Oluwatoyin Folayan, Bridget Haire, & Kristin Peterson, *Ethical Testing of Experimental Ebola Treatments—Letter to the Editor*, 313 JAMA 421, 421 (2015).

[169] Adebamowo, Bah-Sow, Binka, et al, *supra* note 168, at 1423.

[170] CDC, *supra* note 107, at n.p.

during the 2014 outbreak.[171] Therefore, being enrolled in a study that provided supportive care could, in and of itself, be an improvement over an individual's status quo at baseline. While this fact is regrettable, it also weakens the argument made against placebo-controls.

Second, a mere 10% of drugs that are developed make it to clinical trials, and of those, just one in five is ultimately made available to the public.[172] While there may be several explanations for this, one is that clinical research may reveal that a drug is not safe, not effective, or neither safe nor effective. Therefore, it is incorrect to assume—as some opponents of placebo-controls implicitly seem to do—that individuals are necessarily disadvantaged when they do not receive an experimental intervention. They seemingly overestimate the possibility of benefit. Although there was promising evidence from animal models—for instance, ZMapp was 100% effective in studies with rhesus macaques[173] but had not finished typical animal safety testing[174]—there must be caution when inferring the implications for humans from animal data. There is no guaranteed benefit. Moreover, the risks are uncertain. There is a possibility that experimental interventions can make people not just no better off but materially *worse off*, which also appears to be underplayed by those who reject placebo-controls.

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[171] Jon Cohen, *Issues Continue to Dog the Testing of Ebola Drugs and Vaccines*, SCIENCE (Oct. 16, 2014), http://www.sciencemag.org/news/2014/10/issues-continue-dog-testing-ebola-drugs-and-vaccines (last visited Apr. 7, 2016).

[172] Lindsay M. Boyd, *Ebola, The "Right to Try," And Why We Should Care*, FORBES (Aug. 12, 2014), http://www.forbes.com/sites/realspin/2014/08/12/ebola-the-right-to-try-and-why-we-should-care/#35aaec4958fa (last visited Mar. 3, 2016).

[173] Xiangguo Qui, Gary Wong, Jonathan Audet, et al., *Reversion of Advanced Ebola Virus Disease in Nonhuman Primates with ZMapp*, 514 NATURE 47, 47 (2014).

[174] Andrew Pollack, *Ebola Drug Could Save a Few Lives. But Whose?*, NY TIMES (Aug. 8, 2014), http://www.nytimes.com/2014/08/09/health/in-ebola-outbreak-who-should-get-experimental-drug.html?_r=1 (last visited Apr. 7, 2016).

It may be argued in response that when a condition has as high a case fatality rate as EVD, surely, the risks associated with taking an experimental drug cannot be any worse than the risks of having EVD and receiving the standard of care and may, in fact, be better. I concede that reasonable people may—and likely would—prefer to try an apparently promising experimental intervention under such circumstances. Yet, the reported case fatality rate in the 2014 outbreak hovered around 50%, and it is arbitrary line drawing to say that this is the point where it is ethically superior to provide access to an experimental intervention despite the genuine uncertainty about the attendant risks and benefits.

Fourth, individuals do not have a right to access experimental interventions outside of clinical research,[175] nor do they have a right to those interventions conditional on participating in clinical research.[176] Investigators *do not* have a therapeutic obligation to research participants.[177] Recall, the purpose of research is to produce generalizable knowledge for the benefit of future patients.

> [T]he point of medical trials is not to provide the intervention that's medically best for the research subject. It's to establish something that's important—and this point is crucial—for a far larger population and to prevent human catastrophe.[178]

Just as clinical research may justifiably require exposing research participants to procedures that hold no prospect of medical benefit for them personally, research may

[175] *Cf. Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (DC Cir. 2007) (cert denied) (holding that terminally ill adult patients had no fundamental right protected by Due Process Clause to have access to investigational drugs).

[176] I concede that there may be reasons to think participants should have post-trial access if a drug proves to be safe and effective.

[177] Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials*, 33 HASTINGS CENTER REPORT 19, 25 (2003).

[178] Cohen, *supra* note 171, at n.p. (quoting Nir Eyal).

require randomizing some individuals to placebo controls. The burdens and risks randomization imposes on individuals are justified by their social and scientific value. To claim that individuals have a right to a promising experimental intervention is to confuse the ethics of research and care.

An argument can be made that Ebola-ravaged populations have a right to healthcare.[179] It is indisputably unfortunate that existing healthcare systems in countries like Guinea, Liberia, and Sierra Leone cannot meet the pressing need for even the most basic healthcare. It is not, however, the obligation of researchers to fulfill this right. Conditional on engaging in clinical research, researchers may assume obligations to provide ancillary care,[180] to provide a high standard of care to research participants,[181] and also to provide post-trial access to beneficial interventions.[182] It would be wrong, however, to claim that researchers exploit research participants when clinical research offers fair benefits—even if potential research participants' background situation is an unfair one and even if that background situation leads them to feel they have no alternative but to participate in research.[183] The desire to provide clinical benefit to everyone affected by

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[179] *E.g.*, the WHO Constitution enshrines "the highest attainable standard of health as a fundamental right of every human being."

[180] *See generally*, Henry S. Richardson & Leah Belsky, *The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care that Researchers Owe Their Subjects*, 34 HASTINGS CENTER REPORT 25 (2004).

[181] It is an open debate whether researchers can provide the "local" standard of care or whether they should provide the "best" standard of care. *See*, *e.g.*, Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEJM 847 (1997).

[182] *See generally*, Christine Grady, *The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment*, 5 YALE J. HEALTH POLICY, L., & ETHICS 425 (2005) (describing the controversy over post-trial benefits).

[183] *Cf.*, Christine Pace, Franklin G. Miller, & Marion Danis, *Enrolling the Uninsured in Clinical Trials: An Ethical Perspective*, 31 CRITICAL CARE MEDICINE S121 (2003).

EVD should be realized by strengthening health systems, not by prohibiting placebo-controls.[184] Research and strengthening of healthcare systems must be pursued simultaneously.

Finally, when a resource—like an EVD vaccine or treatment—is scarce, clinicians and policymakers face the difficult task of determining how to allocate it among the many individuals who might benefit. Inevitably, rationing will be necessary, and by definition, not everyone who might benefit will be able to have access. It follows from this that there is a real possibility promising experimental interventions might be allocated unfairly. Randomization offers a means to allocate a scare resource fairly.[185] This is preferable to alternate rationing approaches that seem facially to be fair but have disparate impacts on lesser-resourced groups in practice.

To choose but one example, well-off and well-connected patients should not be further privileged in a public health emergency by being prioritized to receive a promising albeit unproven intervention.[186] This would be unfair and could undermine the perceived legitimacy of the public health response to the outbreak. This is not idle speculation. For example, initially, there was only enough ZMapp for seven patients.[187] Many were critical of the fact that two white Americans aid workers, Nancy Writebol and Dr. Kent Brantley,

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[184] *Cf.* Rid & Emanuel, *supra* note 150, at 1844.

[185] *Id.*

[186] Rid & Emanuel, *supra* note 118, at 1897.

[187] Andrew Pollack, *U.S. Will Increase Production of the Ebola Drug ZMapp, but May Not Meet Demand*, NY Times (Oct. 1, 2014), http://www.nytimes.com/2014/10/02/world/us-to-increase-production-of-experimental-drug-but-may-not-meet-demand.html?_r=0 (last viewed Mar. 3, 2016) ("[T]he federal official said it was expected to produce only about 10 to 20 treatment courses by the end of the year, and the same amount every month going forward.").

received ZMapp when comparably sick Africans did not.[188] It was reported that Brantly and Writebol's employer, Samaritan's Purse, only requested two doses of ZMapp, despite the fact that they were treating about 17 other Ebola patients in their Liberian clinic.[189] Although, Mapp Biopharmaceutical Inc., the company that makes ZMapp, says that it filled requests for ZMapp on a first-come, first-served basis,[190] that Writebol and Brantley received the drug served as potent evidence to some that "the life of an African is less valuable."[191]

First-come, first-served—the allocation method favored by many advocates of alternative trial design—may superficially seem like a fair way of distributing a scarce resource, but on further reflection, it is abundantly clear that such an allocation scheme inherently favors the privileged—for example, those who know where to go and have the means to get there—while ignoring other relevant considerations.[192] Randomization within an ethically conducted RCT offers an alternative way to allocate the scarce resource—a drug with the potential (not the promise) to offer an advantage over standard care—fairly among individuals who meet a study's eligibility criteria and who agree to

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[188] *See, e.g.*, Kwei Quartey, *Ebola's Racial Disparity: The Most Effective Treatment for Ebola Might be Having White Skin*, Foreign Policy in Focus (Nov. 26, 2014), http://fpif.org/ebolas-racial-disparity/ (last visited Apr. 7, 2016).

[189] Beth Skwarecki, *Ethical Dilemmas of Giving Ebola Drugs to the People Who Need them Most*, PLOS | Blogs (Sept. 12, 2014), http://blogs.plos.org/publichealth/2014/09/12/last-big-ebola-outbreak/ (last visited Apr. 7, 2016).

[190] Skwarecki, *supra* note 189, at n.p.

[191] Pollack, *supra* note 174, at n.p. (but also quoting an African researcher as saying "It would have been the front-page screaming headline: 'Africans used as guinea pigs for American drug company's medicine" if ZMapp had been tested in Africans first).

[192] *Cf.* Govind Persad, Alan Wertheimer, and Ezekiel J. Emanuel, *Principles for Allocation of Scarce Medical Interventions*, 373 THE LANCET 423, 424 (2009).

contribute to the social good achieved by answering the crucial question: is this intervention, beneficial, neutral, or harmful?

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WHO has cautioned that flare-ups of EVD are to be expected in the wake of the 2014 outbreak,[193] and experts expect there will be other EVD outbreaks in the future.[194] Additionally, we can assume public health emergencies will arise from other threats like Zika virus. It is, therefore, essential to balance individual patient needs and preferences with broader public health considerations. For the reasons outlined above, it is both ethical and necessary to conduct research, including randomized placebo-controlled trials as the opportunity arises, to develop and identify safe and effective drugs and vaccines for use in future outbreaks.

From a research ethics perspective, conducting randomized placebo-controlled trials in the midst of a public health emergency can be justified. Now, let us turn to the formal laws that govern the situation to see how they can advance the goals of drug development, approval, and access in a public health emergency.

[193] WHO, *supra* note 79, at n.p.

[194] Meera Senthilingham, *Are We Ready for the Next Global Epidemic?*, CNN.com, http://www.cnn.com/2015/02/13/health/are-we-ready-for-global-outbreak/ (last visited Mar. 3, 2016).

III. Development, Approval, & Access

A primary reason for FDA involvement in the West African Ebola outbreak was that any drug, device, or biologic must be reviewed by FDA's Center for Drug Evaluation and Research (CDER) and deemed safe and effective before it is marketed in the United States. In this section, I will briefly review the standard process for drug and vaccine development, approval, and marketing/access—the process by which experimental interventions progress from the lab into the hands of consumers—and highlight challenges that arose in the 2014 Ebola outbreak.

A. The Standard Model

The costs of developing a new drug or vaccine are often estimated to exceed $1 billion,[195] and it takes an average of ten years to complete the journey from bench to bedside.[196] This expensive and lengthy process begins with researchers identifying potential biological targets, or structures in the body that will react with a drug compound to produce the desired clinical effect,[197] such as treating EVD. Typically, after starting with thousands of candidate drug compounds, the field is narrowed to one or more "lead compounds," "promising molecule[s] that could influence the target and, potentially,

[195] *See generally*, Joseph A. DiMasi, Henry G. Grabowski, Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 JOURNAL OF HEALTH ECONOMICS 20 (2016).

[196] PhRMA, BIOPHARMACEUTICAL RESEARCH & DEVELOPMENT: THE PROCESS BEHIND NEW MEDICINES, 1 (2015).

[197] *Id.* at 4.

become a medicine."[198] Pre-clinical testing is used to identify those lead compounds that will advance to clinical trials.[199]

FDA does not test the safety or efficacy of drugs itself but instead relies on data supplied by the pharmaceutical company seeking to market the drug.[200] If a company wishes to test a drug, device, or biologic it has developed within the United States, it is first required to contact FDA in order to obtain an Investigational New Drug (IND) application.[201] An IND details the results of preclinical work, including a list of potential side-effects indicated by pre-clinical studies, and provides a detailed clinical trial plan, outlining how, where, and by whom clinical studies will be conducted.[202] While the full safety profile of a novel drug is obviously not known when the company seeks an IND, the company must provide data gathered within the laboratory and in animal testing to support the claim that the drug is safe enough to give to humans.[203] According to recent guidance, FDA's "primary concern [w]hen reviewing an original IND submission or planning for a pre-IND meeting . . . is the safety of the subjects who will receive the drug

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[198] *Id.*

[199] *Id.*

[200] FDA, *How Drugs are Developed and Approved*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ (last visited Jan. 7, 2016).

[201] *See*, *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last visited Jan. 7, 2016).

[202] PhRMA, *supra* note 196, at 11.

[203] FDA, *supra* note 201, at n.p.

during the proposed clinical trial."[204] CDER requires companies to adhere with GCPs, as discussed above.

An IND becomes effective 30 days after the application is submitted, unless FDA imposes a clinical hold.[205] Only after the company has an IND in hand can it begin a multi-phase clinical trial to establish safety (Phase I), to establish efficacy (Phase 2), and to compare the new treatment to the current standard of care in a larger study population (Phase 3).[206] Clinical trials take six to seven years to complete, on average.[207]

Clinical trials that take place outside the United States—as Ebola trials likely would—do not, by contrast, require an IND, although a sponsor may choose to conduct a foreign clinical study under an IND.[208] Companies can, therefore, avoid any kind of preliminary review regarding the adequacy of human subjects protections.[209] However, should a company subsequently seek to market a drug in the United States, "FDA has the legal authority to require sponsors to certify that the data they are using was obtained

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[204] J.S. Bard, *A Taxonomy for Analysing Legal and Ethical Issues Arising When Conducting Human Subject Research Outside the Borders of One's Own Country*, 37 HOUS. J. INT'L L. 1, 32-33 (2015).

[205] § 505(i).

[206] Clinical trials typically are conducted in a series of phases, each designed to answer a distinct research question. Phase 1 studies aim to determine how a drug is metabolized and excreted, establish a safe dosage range, and identify the most frequent side effects. They are usually conducted as one-arm trials in healthy volunteers. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on efficacy. Researchers aim to obtain data on whether the drug works in individuals with the disease or condition of interest. Sometimes, clinical trial phases may be combined (e.g., Phase 1/2) to allow faster development of a new intervention and/or to minimize risks to research participants. NATIONAL INSTITUTES OF HEALTH, *What Are Clinical Trial Phases?*, 18 April 2008, http://www.nlm.nih.gov/services/ctphases.html (last visited Apr. 15, 2016).

[207] PhRMA, *supra* note 196, at 1.

[208] 21 CFR part 312.

[209] Bard, *supra* note 204, at 33.

under the same human subjects protections as would be applicable in the United States."[210] The GCP requirements help to ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

Once clinical trials have been completed, companies then submit a new drug application (NDA) to FDA. A team from CDER—consisting of physicians, statisticians, chemists, pharmacologists, and other scientists—will review the NDA, which contains data from the clinical trials and the proposed labeling[211] and which can run 100,000 pages or more.[212] The 1992 Prescription Drug User Fee Act (PDUFA) established two tiers of review: Standard and Priority.[213] Drugs that offer major advances in treatment or provide a treatment where none previously existed—as would be the case for therapies targeted at Ebola—are designated for Priority Review. The goal for completing a priority review is 6 months. The target for Standard Review is 10 months. If the NDA is approved, the product may be marketed in the United States.

B. Challenges to the Standard Model in the 2014 Outbreak

The traditional model, just outlined, has significant limitations in public health emergencies. As just described, developing a new drug and getting FDA approval is time-

[210] 21 CFR 312.120; 21 CFR 314.106 (governing marketing approval of a new drug based solely on foreign clinical data).

[211] FDA, *How Drugs are Developed and Approved*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm (last visited Jan. 8, 2016).

[212] PhRMA, *supra* note 196, at 14.

[213] FDA, *Frequently Asked Questions about the FDA Drug Approval Process*, http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm279676.htm (last visited Jan. 8, 2016).

consuming. Companies may spend years—or even decades—developing a drug and ushering it through clinical trials before they send an NDA to FDA for review, which then takes six months or more. While this is true of all drugs, there are two key implications in a public health emergency.

First, it is exceedingly unlikely that an entirely new drug will or even can be developed from scratch during an epidemic. Rather, promising compounds must already be far along the development pipeline if they are to have an impact in the near-term. EVD might be somewhat unique among public health threats in that there had already been significant investment in basic research and drug development before the 2014 outbreak in light of concerns the Ebola virus might be used in bioterrorism. Promising compounds are unlikely to be at the ready if a public health emergency is the result of an NTD or comparable illness that is not commercially attractive to pharmaceutical companies or if it is the result of an emerging threat with which we have yet to become familiar.

Second, even if a drug has already been developed including the completion of clinical trials, if it is not yet FDA-approved, it is unlikely that FDA will be able to approve it in time to meet the most pressing patient demands in an outbreak. Taken together, these two considerations suggest it is extremely important to prioritize drug development in inter-outbreak periods and, to the extent possible, to prioritize approval of drugs addressing public health threats.

Further challenges to drug development, approval, and accessibility arose in the 2014 outbreak and are likely to recur in future public health emergencies. First, as mentioned in Section II, it was necessary to conduct clinical trials in the midst of the outbreak because it is unethical intentionally to expose healthy research participants to the

Ebola virus. Yet, conducting research in the midst of an outbreak raised contentious ethical and methodological questions, and people had widely divergent views on how best to proceed. Furthermore, conditions on the ground, discussed in Section I, made both the delivery of care and the conduct of research extremely difficult from a practical perspective.[214] Although the particular challenges that will be confronted on the ground in any given public health emergency cannot be anticipated in advance, there are ethical, methodological, and practical considerations that can and should be anticipated and addressed as part of pre-planning for clinical trials that will transpire in such circumstances.

Second, there were few doses of experimental interventions available for conducting clinical trials, and as the outbreak receded and the number of EVD cases waned, the epidemiologic trajectory made it increasingly difficult to conduct randomized, placebo-controlled trials to show efficacy.[215] As a result, there are still no FDA-approved drugs or vaccines for Ebola. Even if an experimental intervention had successfully passed through clinical trials, however, FDA and other regulatory agencies were likely to confront relatively limited data on safety and efficacy in light of the small size of the patient population. Thus, it is necessary to consider whether alternative approval pathways are appropriate, how data collection standards might be compromised in an epidemic to achieve the appropriate balance between speeding approval and protecting drug consumers, and what, if any, post-marketing trials should be required.

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[214] Although it is beyond the scope of the FDA, I think it is essential for public health that efforts are made to address weak health systems.

[215] Lisa Schnirring, CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY (CIDRAP), *Experts Weigh Challenges, Options for Ebola Vaccine Clearance*, CIDRAP NEWS (May 12, 2015), http://www.cidrap.umn.edu/news-perspective/2015/05/experts-weigh-challenges-options-ebola-vaccine-clearance (last viewed Mar. 4, 2016).

Finally, the prospect of FDA approval raises important questions about who should have access to FDA-approved therapies in a public health emergency and how this will be accomplished. MSF, for example, worried that there was no mechanism to ensure that West African patients would have access to EVD vaccines or treatments. An FDA-approved drug is of little value if it does not get into the hands of those who need it because, for example, they cannot afford it or because it cannot be manufactured in sufficient quantities. Although there are independent normative arguments for why global health inequalities should be addressed, in a public health emergency—particularly in an age when global air transit brings us together and exposes us more widely to health risks—there are additional self-interested reasons to ensure broad access.

* * *

In order for FDA's response to any public health emergency to be maximally effective, the Agency must anticipate and address barriers to development, approval, and access. Here, I have made preliminary, broad recommendations for how this might be accomplished. In the next section, I will look at how FDA in fact used its flexible regulatory framework to respond to these challenges in the 2014 outbreak and make more granular recommendations for how FDA might better respond to future public health emergencies.

IV. FDA and the 2014 Outbreak

During the 2014 Ebola outbreak, FDA worked to "help expedite the development and availability of medical products—such as treatments, vaccines, diagnostic tests, and personal protective equipment—with the potential to help bring the Ebola epidemic in West Africa under control as quickly as possible."[216] FDA's response to the 2014 Ebola outbreak showcases the Agency's panoply of powers and its regulatory flexibility, which enabled it to move relatively rapidly in the context of a public health emergency. Yet, if one considers the response along the dimensions of development, approval, and access, it is clear that there is room for substantial improvement in the response to future public health emergencies.

Unfortunately, more public health emergencies are inevitable. Threats may come from reemerging or from new diseases. The recent pandemic of Zika virus infection in South America, Central America, and the Caribbean is but one example.[217] Although Zika was first discovered in 1947,[218] the present clusters of microcephaly cases and other neurological disorders have occurred in areas newly infected with Zika virus.[219] On

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[216] FDA, *Ebola Response Updates from FDA*, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm410308.htm (last visited Jan. 7, 2016).

[217] Anthony S. Fauci & David M. Morens, *Zika Virus in the Americas — Yet Another Arbovirus Threat*, 374 NEJM 601, 601 (2016).

[218] CDC, *About Zika Virus Disease*, http://www.cdc.gov/zika/about/index.html (last visited Feb. 26, 2016).

[219] WHO, *WHO Statement on the First Meetings of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika Virus and Observed Increase in Neurological Disorders and Neonatal Malformations*, http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/ (last visited Feb. 26, 2016).

February 1, 2016, WHO declared Zika virus a PHEIC.[220] Presently, "[t]here are no vaccines or treatments in advanced development for Zika."[221] Moreover, "[t]here are no commercially available diagnostic tests cleared by the FDA for the detection of Zika virus."[222]

The response to the 2014 EVD outbreak therefore serves as a useful case study from a health policy perspective because it allows us to understand FDA's response to a particular public health emergency and to draw lessons to move forward. I focus on describing and evaluating five steps taken—and one not taken—by FDA. Some of my suggestions simply require FDA to assume a broader role in coordination and planning in inter-emergency periods, while others would require Congressional action to alter or expand the scope of FDA's powers. While one could imagine a range of policy interventions by a broad array of actors—both domestic and international—that would yield improvements along the dimensions of development, approval, and access, this Section focuses more narrowly on what FDA in particular is able to do and how FDA's capacity to respond could be further strengthened.

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[220] *Id.*

[221] FDA, *Zika Virus Response Updates from FDA*, http://www.fda.gov/%20EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm (last visited Feb. 26, 2016).

[222] *Id.*

A. Offering Development Incentives

During the 2014 outbreak, FDA actively used drug development programs to encourage the pursuit of Ebola vaccines and treatments.[223] As discussed in Section I above, many, "including the [Director-General of WHO Dr.] Margaret Chan, have criticized the pharmaceutical industry's lack of investment in investigational treatments for [EVD], saying many companies had likely determined the return on any investment for an Ebola treatment was not worth the development cost."[224] Development incentives are intended to overcome entrenched reluctance to invest in neglected diseases. Unfortunately, the two development incentives at FDA's disposal—the Orphan Drug Act and vouchers for priority review—had clear shortcomings when used in the context of EVD.

1. Orphan Drug Act

The Orphan Drug Act of 1983 was passed to counterbalance market forces and incentivize development of drugs defined by statute as affecting fewer than 200,000 people in the United States.[225] The Act offers pharmaceutical companies a variety of incentives, including market exclusivity, tax credits, and research grants.[226] These are "push" and

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[223] FDA, *Ebola Response Updates from FDA*, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm410308.htm (last viewed Jan. 8, 2016).

[224] Alexander Gaffney, *US Senate Unveils Major Changes to FDA Program in Hopes of Fighting Ebola* (Nov. 12, 2014), http://www.raps.org/Regulatory-Focus/News/2014/11/12/20724/US-Senate-Unveils-Major-Changes-to-FDA-Program-in-Hopes-of-Fighting-Ebola/ (last visited Mar. 4, 2016).

[225] FDA, The Orphan Drug Act (as amended), http://www.fda.gov/orphan/oda.htm.

[226] *Id.*

"pull" incentives for drug development. Whereas "push" is focused on the cost-side of the profit equation, "pull" is focused on the revenue side: "push" incentives serve to lower the logistical and financial barriers to entry, while "pull" incentives increase the likelihood that there will be a sufficient return on investment once products reach market.[227] In 2014, FDA granted orphan designation to products being developed to treat EVD, including ZMapp.[228]

The Department of Health and Human Services (HHS) has previously concluded that the Orphan Drug Act "unquestionably stimulated the development [of drugs] for rare diseases,"[229] particularly for rare genetic diseases affecting Americans.[230] This success is partially attributable to the surprising profitability of orphan drugs. Eighteen blockbuster drugs—those with global annual sales of greater than $1 billion—were approved solely as orphan drugs within the United States.[231] The profitability of orphan drugs has been "driven [in part] by a strong disposition among healthcare purchasers in high-income

[227] Christopher-Paul Miline & Joyce Tait, *Evolution Along the Government-Governance Continuum: FDA's Orphan Products and Fast Track Programs As Exemplars of "What Works" for Innovation and Regulation*, 64 FOOD & DRUG L. J. 733, 737 (2009).

[228] Jason Millman, *Why the Drug Industry Hasn't Come up with An Ebola Cure*, THE WASHINGTON POST (Aug. 13, 2014), https://www.washingtonpost.com/news/wonk/wp/2014/08/13/why-the-drug-industry-hasnt-come-up-with-an-ebola-cure/ (last visited Mar. 4, 2016).

[229] OFFICE OF INSPECTOR GENERAL, HHS, THE ORPHAN DRUG ACT—IMPLEMENTATION AND IMPACT, at 7 (2001). *See, also*, FDA, *CDER Approved Many Innovative Drugs in 2014,* http://blogs.fda.gov/fdavoice/index.php/2015/01/cder-approved-many-innovative-drugs-in-2014/ (last visited Jan. 8, 2016) (noting that 17 of the 41 novel new drugs were approved to treat rare diseases).

[230] Arnold & Pogge, *supra* note 248, at 225.

[231] M. Ian Phillips, *Big Pharma's New Model in Orphan Drugs and Rare Diseases*, 1 Expert Opinion on Orphan Drugs 1, 2 (2012).

countries to pay for these drugs at high prices."[232] These drugs can be prohibitively costly for patients without means.

Yet, the effect of the Orphan Drug Act on the development of drugs for NTDs and other neglected public health threats has been markedly less impressive. Some have concluded that the Act's generous subsidies "are not enough when prospective gains from commercialization are poor."[233] The Food and Drug Administration Amendments Act of 2007 (FDAAA), which created the priority review voucher (PRV) program, discussed further below, was passed to address this deficit and create a greater "pull" specifically for NTDs.[234]

With respect to the Orphan Drug Act, the pharmaceutical industry has consistently identified the 7-year marketing exclusivity provision as the Act's most important "pull" lever.[235] This fact led some to advocate during the 2014 EVD outbreak for extending the marketing exclusivity period from 7 to 10 years to further strengthen incentives for development of Ebola drugs.[236] Extending the marketing exclusivity period, which would require an act of Congress, would in theory create some additional "pull." Yet, it is unclear that this amendment to the Act would make any meaningful difference with respect to current or future public health threats because, "[f]or things like Ebola, there is no clear

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[232] Arnold & Pogge, *supra* note 248, at 225.

[233] *Id.*

[234] *Id.*

[235] Gilbert Grimm & Len M. Nichols, *Ebola Crisis of 2014: Are Current Strategies Enough to Meet the Long-Run Challenges Ahead?*, 105 AM. J. PUB. HEALTH e8, e9 (2015).

[236] *Id.*

buyer other than the government."[237] Beyond the government, the market was small and likely unable to pay for any saleable product. Under the circumstances it would be more effective for Congress to introduce advanced market commitments (AMCs). AMCs have not been used for NTDs,[238] but they could incentivize development by setting a minimum price and quantity for purchase, conditioned on receipt, for example, of orphan drug designation and FDA approval.

In the case of NTDs and other public health threats, it is doubtful that orphan drug designation currently offers sufficient "push" incentives for the development of interventions to address public health threats either. Additional "push" solutions need to be identified. While FDA could potentially administer these, for example, by deepening the tax credits and research grants tied to orphan drug designation, it would be preferable to look beyond FDA and increase federal research funds to support development of vaccines and treatments for public health threats.[239] Given its firsthand knowledge of the

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[237] Brendan Greeley & Caroline Chen, *How the U.S. Screwed Up in the Fight Against Ebola*, BLOOMBERG BUSINESS WEEK (Sept. 24, 2014), http://www.bloomberg.com/news/articles/2014-09-24/ebola-drug-zmapps-development-delayed-by-pentagon-agency (last visited Apr. 12, 2016).

[238] Sarika Bansal, *How Pharmaceutical Companies Can Help Take the 'Neglected' Out of Neglected Tropical Diseases (NTDs)*, FORBES (Nov. 9, 2011), http://www.forbes.com/sites/sarikabansal/2011/11/09/neglected-tropical-disease-pharmaceutical-companies/2/#2bfc6d326fd1 (last visited Apr. 14, 2016).

[239] As discussed above, NIAID, the Department of Defense, and the Biomedical Advanced Research and Development Authority, within HHS, have supported research relevant to Ebola; this includes basic research as well as getting drugs into clinical trials. However, funding has been erratic, which has led to "delays in many programs critical to biodefense." James J. Carafano, Charlotte Florance, & Daniel Kaniewski, THE EBOLA OUTBREAK OF 2013-2014: AN ASSESSMENT OF U.S. ACTIONS, THE HERITAGE FOUNDATION, 22 (2015). Appropriations for the development of medical counter-measures need to be larger as well as more consistent. When no effective market exists, government contracting may constitute "a necessary complementary incentive" to intellectual property. Henry G. Grabowski, Joseph A. DiMasi, & Genia Long, *The Roles of Patents and Research And Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFFAIRS 302, 308 (2015). Furthermore, there needs to be coordination between the various arms of the federal government working to address these problems so as to avoid inefficiencies.

shortcomings of orphan designation, FDA should advocate for these changes as a complement to its own efforts.

2. Priority Review Voucher Program

On December 16, 2014, President Obama signed the Adding Ebola to the FDA Priority Review Voucher Program Act into law.[240] This was an amendment to the FDAAA, which was intended to provide incentives to companies to invest in NTDs. The FDAAA added new section 524 to the FD&C Act, which "authorizes FDA to award priority review vouchers (PRV) to sponsors of certain tropical disease product applications that meet the criteria specified by the Act."[241]

An *ex post* reward for developers, the PRV is a transferable voucher for future Priority Review on a subsequent drug or biologic brought before the FDA. The PRV program seeks to "incentivize the development of tropical disease products without burdening taxpayers or delaying generic entry."[242] Compared to the Orphan Drug Act,

> which significantly subsidizes the inputs of innovation ('push'), the [PRV] program rewards only the successful outputs of the pharmaceutical R&D process. The vouchers, therefore, serve exclusively as a pull mechanism to stimulate the

[240] Alexander Gaffney, *Obama Signs Special Ebola Incentive Program into Law*, http://www.raps.org/Regulatory-Focus/News/2014/12/18/20999/Obama-Signs-Special-Ebola-Incentive-Program-Into-Law/ (last visited Mar. 4, 2016).

[241] FDA, *Guidance for Industry: Tropical Disease Priority Review Vouchers* (Draft Guidance Oct. 2008), *http://www.fda.gov/downloads/Drugs/.../Guidances/UCM080599.pdf.*

[242] Lesley Hamming, *The Promise of Priority Review Vouchers As A Legislative Tool to Encourage Drugs for Neglected Diseases*, 11 DUKE L. & TECH. REVIEW 390, 394 (2013).

development of drugs that might not otherwise be brought to market due to insufficient sales potential.[243]

PRVs provides a significant advantage to drug manufacturers, as they entitle their holder to a 6-month priority review by FDA, rather than the standard 10-month review.[244] It has been estimated that a PRV "would be worth more than $300 million for a potential blockbuster drug" because the drug reaps the benefit of entering the market significantly earlier.[245] Alternatively, a PRV may be transferred or sold to another sponsor,[246] which can also be incredibly lucrative. For instance, Sanofi paid $245 million for a PRV in 2015.[247]

EVD was initially omitted from the FDAAA because FDA consulted with WHO's Department of Control of Neglected Tropical Diseases when drafting its initial list of eligible NTDs in 2006-07, and WHO does not recognize EVD as an NTD because of its historically low morbidity and mortality.[248] Ebola serves as a potent example that the PRV program is too narrow as currently written to address burgeoning public health threats, which may not be "classic" NTDs, the characteristics of which were addressed at some length in Section I. It has been suggested that the PRV program should be expanded to

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[243] Cameron Graham Arnold & Thomas Pogge, *Improving the Incentives of the FDA Voucher Program for Neglected Tropical* Diseases, 21 BROWN J. WORLD AFF. 223, 225 (2014-2015).

[244] GAO Highlights, *Rare Diseases: Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program* (Mar. 2016), http://www.gao.gov/assets/680/675544.pdf (last visited Mar. 4, 2016), at 1.

[245] Hamming, *supra* note 242, at 398–399.

[246] FDA, *supra* note 241, at 1.

[247] PMLiVE, *Sanofi Pays $245m for FDA Priority Review Voucher*, May 28, 2015, http://www.pmlive.com/pharma_news/sanofi_pays_$245m_for_fda_priority_review_voucher_744940 (last viewed Mar. 4, 2016) ("This is the third time a PRV has changed hands and, with their value escalating each time, the deals clearly illustrate the competitive benefits that can accrue from even a small lead in the marketplace.").

[248] Arnold & Pogge, *supra* note 243, at 228.

include biodefense products,[249] a category that would include Ebola, and could also be relevant to some future public health emergencies. While potentially beneficial, this eligibility expansion is an incomplete solution at best.

The delayed expansion of the PRV program to include Ebola could be characterized as needlessly hampering FDA's ability to incentivize EVD research. Incentivizing research with PRVs only after the outbreak began was unlikely to make any meaningful difference in the short-term (i.e., the lifecycle of the 2014 outbreak). The failure to include EVD sooner—that is, in the FDAAA, was faulted for stalling "auspicious early research" into EVD drugs and vaccine candidates due to a lack of interest from the private sector.[250] Yet, given the low overall number of people affected by EVD before the 2014 outbreak began, discussed in Section I, this is probably overstating the effect that PRVs would have had. A PRV would effectively have been the lone commercial reward for any Ebola-specific product developed because there was, in effect, no market for such products. The approximately $300 million value of the PRV would likely have been insufficient on its own for pharmaceutical companies, given that, as discussed in Section III, the costs of developing a new drug or vaccine are often estimated to exceed $1 billion.

More broadly, PRVs have been criticized as "an inefficient and potentially dangerous way of encouraging research into [neglected] tropical diseases."[251] For large

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[249] INSTITUTE OF MEDICINE (IOM) FORUM ON MEDICAL AND PUBLIC HEALTH PREPAREDNESS FOR CATASTROPHIC EVENTS & IOM FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION, THE PUBLIC HEALTH EMERGENCY MEDICAL COUNTERMEASURES ENTERPRISE: INNOVATIVE STRATEGIES TO ENHANCE PRODUCTS FROM DISCOVERY THROUGH APPROVAL: WORKSHOP SUMMARY (2010).

[250] Arnold & Pogge, *supra* note 243, at 229.

[251] Aaron S. Kesselheim, *Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers*, 359 NEJM 1981, 1981 (2008); *but see,* Jeffrey Moe, Henry Grabowski, & David Ridley, *Correspondence: FDA Review Vouchers*, 360 NEJM 837 (2009) (replying to Kesselheim).

pharmaceutical companies, PRVs do not "directly connect the incentive with the innovation . . . [because] the voucher's value depends on the success of potential 'blockbuster' drugs that are currently in their pipelines, which is far from assured."[252] Small companies, which conduct the majority of tropical disease research, will often be unable to use their vouchers themselves,[253] though it can, as just mentioned, be lucrative to sell them.

A further challenge of "pull" funding instruments like PRVs is that they assume a drug or vaccine developer has the funds available up-front to invest in initial R&D and clinical development.[254] Yet, that will not always be the case, particularly given the role for small companies, just mentioned. "Push" mechanisms—like funding of clinical trials—will also be needed to provide an urgently needed infusion of funds.[255] Thus, the PRV program should be understood as a complement to other mechanisms for encouraging drug development and not a stand-alone solution to the problem of NTDs.

Even if we assume, however, that the lure of PRVs is sufficient to drive the development of new drugs for NTDs, EVD, or other public health threats that might be added to the PRV program and that companies have or can obtain the necessary up-front funds, this can be viewed as only a first step in providing a drug to combat a disease. The mere existence of drugs for neglected diseases does not ensure that those who need them will have access to them. In order to receive a PRV, a company must only get FDA approval

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[252] Kesselheim, *supra* note 251, at 1981.

[253] *Id.* (noting the lack of transparency in these transactions is undesirable).

[254] *See* Peter J. Hotez, Maria Elena Bottazzi, & Ulrich Strych, *New Vaccines for the World's Poorest People*, 67 ANNU. REV. MED. 405, 412–413 (2016).

[255] *Id.* at 413.

for its new drug. The company is not required to facilitate access to the drug for those who need it.[256] In practice, sustainable access to drugs that have earned PRVs for their developers has not been achieved in developing countries.[257] Experience prompted MSF to describe the addition of EVD to the PRV program as "much-welcome" but simultaneously to express concern that there was still no "way to ensure that patients, governments and treatment providers like MSF, will have affordable and appropriate access to the potential resulting Ebola medicines and vaccines."[258]

FDA has already—and for unrelated reasons—asked for changes to the PRV program.[259] It should request further changes in the program to enhance the response to future public health emergencies. In particular, Congress should make explicit demands that companies seeking a PRV demonstrate that reasonable efforts have been made to facilitate access to any new drug.[260] This could be accomplished by having the developer manufacture and market the drug itself at an affordable price or by licensing the drug to another manufacturer to achieve the same result.[261] Such changes to the legislation would further align the economic incentives of drug developers with broader public health needs.

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[256] Arnold & Pogge, *supra* note 243, at 227–228.

[257] *Id.* at 228.

[258] MSF, *Ebola to Be Added to List of Neglected Diseases Eligible for US Government Research and Development Incentive*, http://www.msfaccess.org/our-work/neglected-diseases/article/2341 (last visited Mar. 4, 2016).

[259] John Carroll, *That Priority Review Voucher Program? The FDA Hates It*, FIERCEBIOTECH (Mar. 3, 2016), http://www.fiercebiotech.com/story/priority-review-voucher-program-fda-hates-it/2016-03-03 (last visited Mar. 4, 2016) ("FDA says it's been a bust, forcing regulators to prioritize drugs that neither are focused on a key health issue nor offer all that much in terms of added safety or efficacy. It's also a chore to keep up with the mandate.").

[260] Arnold & Pogge, *supra* note 243, at 230–231.

[261] *Id.*

B. Granting Fast Track Status

Fast Track is "a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need."[262] Fast Track programs have previously been used to address bioterror threats, pandemic threats, and neglected diseases.[263] FDA granted Fast Track status to several Ebola treatments, including TKM-Ebola in 2014[264] and ZMapp in 2015.[265]

A drug company must request Fast Track designation. FDA reviews the request and makes a decision within sixty days. A drug that receives Fast Track designation is eligible for more frequent meetings with FDA to discuss the drug's development plan; more frequent communication from FDA; eligibility for Accelerated Approval and Priority Review (if certain criteria are met); and Rolling Review.[266] By opening the lines of communication between the drug company and FDA, Fast Track designation "assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients."[267] Although development times are comparable to other newly approved

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[262] FDA, *Fast Track*, http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm (last visited Mar. 8, 2016).

[263] Miline & Tait, *supra* note 227, at 747.

[264] Anna Prior, *FDA Fast Tracks Tekmira's Ebola Drug*, THE WALL STREET JOURNAL (Mar. 5, 2014).

[265] Debra Goldschmidt, *Experimental Ebola Drug ZMapp Gets Fast Track Status from FDA*, CNN, September 17, 2015.

[266] FDA, *supra* note 262, at n.p.

[267] *Id.*

drugs and biologics, Fast Track-designated products have shorter median approval times.[268]

Because of the challenges associated with developing a drug or vaccine for a public health emergency, the need for frequent consultation with FDA is likely. Formalizing this process—that is, getting Fast Track designation—can be an "important milestone" for a company.[269] This is not merely a formality. While orphan designation, just addressed, fosters innovation directly, Fast Track designation "arguably does so indirectly."[270]

> An econometric analysis of fast track suggests that shortening the arduous path from lab bench to pharmacy shelf can have the following effects: 1) earlier access to cash returns; 2) cuts in development costs; 3) allowing a sponsor to gain first mover advantage, i.e., engender brand loyalty resulting in higher and longer market share; and 4) earlier launch, and thus longer effective patent life or period of market exclusivity protection.[271]

Unsurprisingly, Fast Track status is often pursued in conjunction with other development incentives, like orphan drug designation and PRVs.[272]

The Fast Track process is beneficial to speeding FDA approval, which is a necessary if not sufficient condition for access, and will work best when public health goals are clear. Obviously, such clarity may be difficult to achieve when emerging threats are broadly anticipated but the particulars are unknown. Nevertheless, looking forward, it is important

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[268] Miline & Tait, *supra* note 227, at 741.

[269] Maggie Fox, FDA Fast-Tracks Experimental Ebola Drug ZMapp, NBC News (Sep. 21, 2015), http://www.nbcnews.com/storyline/ebola-virus-outbreak/ebola-drug-zmapp-gets-fda-fast-track-n429156 (last visited Apr. 14, 2016).

[270] Miline & Tait, *supra* note 227, at 744.

[271] *Id.* at 741.

[272] *Cf.* Fox, *supra* note 269, at n.p.

that FDA clearly communicate with drug developers during inter-epidemic periods and suggest they apply for Fast Track designation to direct its efforts towards advanced planning for accelerating the development and testing of promising interventions when epidemic situations arise.[273] During the 2014 outbreak it was said that

> several vaccines and drugs . . . have shown promise in animal studies, and some are so far along that human clinical trials could probably have begun at any time in the past several years . . . . Some of these vaccines have been stuck in this position for 10 years.[274]

FDA should work closely with sponsors to ensure that promising products are not "stuck" when opportunity knocks. Fast Track designation offers one existing but thus far underutilized means of achieving this.

C. Providing General Guidance on Trial Design

FDA acknowledges that the EVD "epidemic has highlighted the importance of being able to rapidly evaluate investigational products during a public health emergency, including in resource limited settings."[275] In an important piece of advocacy, officials at FDA made the case for RCTs when evaluating Ebola therapies in the NEW ENGLAND JOURNAL

[273] J.J. Farrar & P. Piot, *The Ebola Emergency—Immediate Action, Ongoing Strategy*, 371 NEJM 1545, 1545 (2014).

[274] Schlanger & Wolfson, *supra* note 102, at n.p. (internal quotation marks omitted).

[275] FDA, *Public Workshop - Clinical Trial Designs for Emerging Infectious Diseases*, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm466153.htm (last visited Mar. 7, 2016).

OF MEDICINE in December 2014.[276] Agency officials also outlined the FDA perspective on evaluating medical products for EVD—separating out considerations for vaccines and therapeutic products—in an article in CLINICAL TRIALS.[277] The officials underscored the need for "scientifically valid studies that are ethically acceptable and well conducted to provide timely, interpretable data."[278] This advice was so general as to verge on unhelpful.

Additionally, in November 2015, FDA held a workshop in partnership with NIAID, CDC, and the HHS Office of the Assistant Secretary for Preparedness and Response to discuss "the scientific, ethical, and practical issues considered in the choice of specific trial designs, and the generalizability of these designs for other types of emerging infectious diseases."[279] FDA is working to develop "a flexible, innovative and adaptive clinical trial protocol that will provide a mechanism for product sponsors and investigators to evaluate multiple investigational products under a common protocol."[280] I welcome such efforts and encourage FDA to continue to pursue them beyond the 2014 Ebola outbreak.

"Platform trials"—clinical trials with a master protocol in which multiple treatments are evaluated simultaneously—have been planned and/or implemented in a variety of

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[276] E. Cox, L. Borio, & R. Temple, *Evaluating Ebola Therapies—The Case for RCTs*, 371 NEJM 2350 (2014); *see also FDA Officials Call for Ebola RCTs*, 22 No. 5 GUIDE TO GOOD CLINICAL PRACTICE NEWSL. 16 (2014).

[277] Estelle Russek-Cohen, Daniel Rubin, Dionne Price, Wellington Sun, Edward Cox, & Luciana Borio, *A US Food and Drug Administration Perspective on Evaluating Medical Products for Ebola*, 13 CLINICAL TRIALS 105, 105 (2016).

[278] *Id*.

[279] *Id.*

[280] Luciana Borio, *Examining Medical Product Development in the Wake of the Ebola Epidemic*, www.hhs.gov/asl/testify/2014/11/t20141119b.html (last visited Apr. 12, 2016).

diseases, including Ebola.[281] Platform trials have the advantage of allowing for standardized data collection and providing for a common statistical analysis plan.[282] As a result, they "can find beneficial treatments with fewer patients, fewer patient failures, less time, and with greater probability of success than a traditional two-arm strategy."[283] Moreover, it is easier to show the comparative effectiveness of different experimental interventions in platform trials.[284] Such trials have the additional advantage of having only one control group with numerous experimental arms, which satisfies the need for methodological rigor while also minimizing placebo use, both of which were addressed in Section II, above. A potential drawback to platform trials is that they "require considerable coordination of efforts that may be difficult to achieve during an outbreak setting."[285] Additionally, pharmaceutical companies might not naturally gravitate to such a trial design because the approach is inherently cooperative, while their industry is inherently competitive.

It is important that FDA lend its weight to such a plan. FDA has actively sought to coordinate and facilitate the research and development process for regulatory approval, and it is likely to play a significant role in reviewing drug and vaccine candidates in future

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[281] Benjamin R. Saville & Scott M. Berry, *Efficiencies of Platform Clinical Trials: A Vision of the Future*, CLINICAL TRIALS: DOI: 10.1177/1740774515626362, 1–2 (2016).

[282] *Id.* at 7.

[283] *Id.*

[284] Judy Stone, *Are Placebos Ethical In Ebola Trials?*, FORBES (Dec. 30, 2014), http://www.forbes.com/sites/judystone/2014/12/30/are-placebos-ethical-in-ebola-trials/#14a3361945e5 (last visited Apr. 12, 2016).

[285] Lori E. Dodd, Michael A. Proschan, Jacqueline Neuhaus, et al., *Design of a Randomized Controlled Trial for Ebola Virus Disease Medical Countermeasures: PREVAIL II, The Ebola MCM Study*, J. INFECT. DIS.: doi: 10.1093/infdis/jiw061, 7 (2016).

public health emergencies. Therefore, FDA can serve as a hub, coordinating between sponsors and investigators. Furthermore, FDA must continue to collaborate with NRAs and WHO to come up with broad-based solutions that are acceptable to all stakeholders—for example, citizens of developing countries where research is conducted. FDA can and should use the inter-epidemic period to address transparently the practical, scientific, and ethical issues presented by such a trial-design—many of which were addressed in Section II—and build consensus behind these choices.

I stress that the process of consensus-building will require FDA to examine and synthesize the emerging literature on conducting research in public health emergencies.[286] Understandably, a number of concerns were raised about researchers' ability to adhere to ethical principles while conducting research in the midst of the 2014 Ebola outbreak.[287] The urgent demand for use of experimental interventions coupled with the complex dynamics of the outbreak itself made it difficult to be confident that standard subject

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[286] *E.g.*, Philippe Calain, Nathalie Fiore, Marc Poncin, and Samia A. Hurst, *Research Ethics and International Epidemic Response: The Case of Ebola and Marburg Hemorrhagic Fevers*, PUBLIC HEALTH ETHICS (2009); Daniel G. Bausch, A.G. Sprecher, Benjamin Jeffs, and Paul Boumandouki, *Treatment of Marburg and Ebola Hemorrhagic Fevers: A Strategy for Testing New Drugs and Vaccines Under Outbreak Conditions*, 78 ANTIVIRAL RESEARCH 150 (2008); CIOMS, REVISION OF CIOMS 2002 INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS: DRAFT GUIDELINES (2015), available at http://www.cioms.ch/images/stories/guidelines_demo/AllGuidelines-1-25.pdf (last visited Jan. 4, 2016) (Proposed Guideline 20, Research in Disaster Situations).

[287] Ebola was discussed at Meeting Twenty of the Presidential Commission for the Study of Bioethical Issues. PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES, *Ebola*, February 5, 2015, http://www.bioethics.gov/taxonomy/term/213; Laura Seay, Ebola, Research Ethics, and the ZMapp Serum, The Washington Post, August 6, 2014, http://www.washingtonpost.com/blogs/monkey-cage/wp/2014/08/06/ebola-research-ethics-and-the-zmapp-serum/; Hantel & C.O. Olopade, *("*The belief that informed consent is understood by patients naive to advanced health care, especially in an epidemic, is cavalier."); Arthur Caplan, *Bioethicist: Experimental Ebola Treatment Endorsed, but Who Gets It?*, NBC NEWS, August 12, 2014, http://www.nbcnews.com/storyline/ebola-virus-outbreak/bioethicist-experimental-ebola-treatment-endorsed-who-gets-it-n178691 (asking if third parties can consent for children, persons with poor education, prisoners, or others who might wish to try or be eligible for unapproved drugs); Tracy Hampton, *Largest-Ever Outbreak of Ebola Virus Disease Thrusts Experimental Therapies, Vaccines into Spotlight*, JAMA (2014) (noting that "obtaining adequate informed consent would be a [sic] challenging in resource-limited settings").

protections were in place. Such concerns are particularly potent when the potential population of research participants is vulnerable, and the perceived legitimacy of clinical research may affect the uptake of clinical care.[288]

Additionally, FDA must confront the ethical challenges that surround the inclusion of vulnerable populations in clinical research conducted during public health emergencies. For example, it will be important to enroll pregnant women in Zika-related drug and vaccine trials. A pregnant woman can pass Zika virus to her fetus, and CDC has concluded that Zika is a definitive cause of birth defects.[289] While it is essential to include these populations in clinical trials, their inclusion introduces legal and ethical wrinkles into trial design that should be resolved proactively and transparently.

FDA can—and must—continue to play an active role in ensuring adequate protections for research participants in public health emergencies. While it has the power to require adherence to GCPs in domestic and foreign trials used for getting FDA approval, additional constraints on clinical research conducted in public health emergencies should be considered.

[288] *E.g.*, Pollack, *supra* note 174, at n.p.

[289] Liz Szabo, *Study: Zika May Affect Babies Even in Later Stages of Pregnancy*, USA Today (Apr. 14, 2016), http://www.usatoday.com/story/news/2016/04/13/study-zika-may-affect-babies-even-later-stages-pregnancy/82987460/ (last viewed Apr. 14, 2016).

D. Considering Alternative Approval Pathways

FDA considered use of alternative drug efficacy testing pathways as it became apparent that conducting an RCT would be infeasible due to the epidemiological trajectory of the 2014 outbreak.[290] If conditions do not allow Phase 3 trials to proceed, FDA has two other licensing pathways: accelerated approval[291] and the "animal rule."[292]

FDA's power to grant accelerated approval comes out of the

> Food and Drug Administration Safety Innovations Act (FDASIA) [of 2012]. Section 901 of FDASIA amends the [FD&C] Act . . . to allow the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.[293]

Meanwhile, use of the animal rule

> as a regulatory pathway to approval is intended for drugs developed to ameliorate or prevent serious or life-threatening conditions caused by chemical, biological, radiological, or nuclear substances regardless of whether the substances are considered potential threat agents for deliberate exposure (e.g., nerve agent, *Bacillus anthracis*) or threats to individuals' health from accidental exposure (e.g., emerging infectious pathogens, snake venom, industrial chemicals), provided that

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[290] For example, the Agency's Vaccines and Related Biological Products Advisory Committee (VRBPAC) considered "whether, if an Ebola vaccine was approved through an alternative pathway, what approaches postmarketing studies would need to show vaccine benefits." Schnirring, *supra* note 215, at n.p.

[291] 21 CFR 601.40-41 (biologics).

[292] 21 CFR 314. 600-650 (drugs); 21 CFR 601.90-91 (biolgics).

[293] FDA, *Accelerated Approval*, http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm (last visited Mar. 4, 2016) ("A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM).").

> human efficacy studies are not ethical and field trials to study effectiveness of the drug are not feasible.[294]

For FDA to apply the animal rule, the agency would first have to determine that approval is not possible through traditional or accelerated approval.[295] Use of the animal rule can be considered on a product-by-product basis.[296]

Like traditional approval, accelerated approval and animal rule approval, "share the same requirements for demonstration of safety and consistency of manufacture."[297] Additionally, approval under either accelerated approval or the animal rule pathway would require that post-licensure studies be conducted in the future to verify and describe clinical benefit.[298]

The 2014 outbreak has been declared "stopped" by WHO. It has been observed that

> [w]ith the apparent end of the Ebola epidemic in West Africa, public- and private-sector attention is quickly turning to the next public health crisis, leaving Ebola vaccines at the stage of investigational products in clinical trials, which may be inadequate for rapid deployment when the next Ebola outbreak occurs.[299]

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[294] HHS, FDA, *Product Development Under the Animal Rule: Guidance for Industry* (May 2015), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf.

[295] WELLCOME TRUST & CIDRAP, *supra* note 121, at 12.

[296] *Id.*

[297] Doran L. Fink, *Approaches to Demonstrating Effectiveness: Considerations for Ebola Vaccines* (May 12, 2015), at 3, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM451561.pdf (last visited Mar. 4, 2016).

[298] WELLCOME TRUST & CIDRAP, *supra* note 121, at 12.

[299] *Id.*

It remains to be resolved whether alternative approval pathways are feasible and appropriate.[300] Recognizing that sporadic outbreaks, uncertain epidemiologic trajectories, small patient populations, and clinical uncertainty may make it difficult to collect data in epidemics the Agency should be transparent about the conditions under which alternative pathways will be considered and what the tradeoffs are between certainty and access. Requirements and expectations for nontraditional approval pathways should be clearly defined by FDA and, ideally, harmonized across NRAs.[301] FDA could assume a leadership role in such efforts.

E. Authorizing Compassionate Use of Drug Products

"Compassionate use," or expanded access, "is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options."[302] FDA has mechanisms for allowing expanded access to individuals, intermediate-size patient populations, and widespread populations.[303] During the Ebola outbreak, the focus was on expanding individual access.

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[300] In the case of vaccines, there is "[n]o scientifically well-established immunologic marker that predicts protection" against EVD. Fink, *supra* note 297, at 5.

[301] WELLCOME TRUST & CIDRAP, *supra* note 121, at 23.

[302] FDA, *IND Applications for Clinical Treatment (Expanded Access): Overview*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm351748.htm (last visited Jan. 8, 2016). *See also*, 21 CFR 312 Subpart I.

[303] FDA, *Expanded Access: Information for Patients*, http://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm20041768.htm#different-types (last visited Mar. 4, 2016).

A physician can request to use an investigational product for a single patient via an Emergency Investigational New Drug (EIND) application.[304] An EIND may be granted if the "physician considers the product may be urgently needed for the patient's serious or life-threatening condition; no satisfactory alternative therapy is available; and the patient cannot receive the product through any existing clinical trials or expanded access protocols."[305] An EIND request can be authorized by the Agency "within a very short period of time, depending on the urgency of the situation and the nature of the available information."[306] FDA cannot, however, compel a drug company to give a patient access to an experimental drug; the company that produces the drug must agree to provide it.

In 2014, EINDs were granted for several investigational therapeutic candidates, such as ZMapp, TKM-Ebola, and Brincidofovir.[307] As discussed in Section II, compassionate

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[304] In February 2015, FDA released a draft guidance document, *Individual Patient Expanded Access Applications: Form 3926*, announcing a move toward a "streamlined alternative" for submitting individual patient expanded access applications. FDA estimated that the new form, "when finalized, will require only eight elements of information and a single attachment. We estimate that physicians will be able to complete the finalized version of the form in just 45 minutes, as compared to the 100 hours listed on the previous form." Alexander Gaffney, *From 100 Hours to 1: FDA Dramatically Simplifies its Compassionate Use Process* (Feb. 4, 2015), http://www.raps.org/Regulatory-Focus/News/2015/02/04/21243/From-100-Hours-to-1-FDA-Dramatically-Simplifies-its-Compassionate-Use-Process/ (last visited Mar. 4, 2016).

[305] Emergency Investigational New Drug (EIND) Applications for Antiviral Products, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm090039.htm (last accessed Jan. 8, 2016).

[306] Alexander Gaffney, *Regulatory Explainer: What You Need to Know About the Regulation of Ebola Treatments*, Aug. 7, 2014, http://www.raps.org/Regulatory-Focus/News/2014/08/07/19977/Regulatory-Explainer-What-You-Need-to-Know-About-the-Regulation-of-Ebola-Treatments/ (last viewed Mar. 7, 2016).

[307] *FACTSHEET: Update on the Ebola Response* (Dec. 2, 2014), https://www.whitehouse.gov/the-press-office/2014/12/02/fact-sheet-update-ebola-response (last visited Jan. 8, 2016).

There were concerns that, due to the high-profile nature of the Ebola outbreak, Brantley, Whitebol, and others were able to circumvent the mandated process quickly. Boyd, *supra* note 172, at n.p. The Goldwater Institute, a libertarian think tank which developed the model for "Right-to-Try" legislation adopted in several states, filed a Freedom of Information Act request with FDA seeking information about the internal decision-making process used by FDA to allow Brantly and Writebol access to ZMapp. *FDA Denies FOIA Request on Use of Experimental Ebola Drug*, 22 No. 3 GUIDE TO GOOD CLINICAL PRACTICE NEWSL. 9. Significantly, the Institute

use is potentially at odds with conducting socially valuable, scientifically rigorous research to benefit future patients. For example, two American aid workers, Brantley and Writebol, were transferred from West Africa to Emory University Hospital in Atlanta, Georgia, where they received ZMapp under a compassionate use exemption from FDA.[308] Brantley and Writebol ultimately recovered.[309] While their recoveries were encouraging, it was not possible to reach a sound conclusion about ZMapp's safety or efficacy on the basis of Brantley's and Writebol's experiences alone.[310] At the time, Dr. Bruce Ribner, director of Emory's Infectious Disease Unit acknowledged, "There is no prior experience with [ZMapp], and frankly, we do not know whether it helped them, whether it made no difference, or even, theoretically if it delayed their recovery."[311]

Compassionate use provided no clear evidence that experimental interventions like ZMapp were actually superior to supportive care, nor did compassionate use foreclose on the possibility that they were inferior. Yet, in the 2014 outbreak, quantitates of

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"never objected to the fact that the missionaries received the medication, but has questioned whether the agency provided favorable treatment and sought to obtain FDA records about the ZMapp decision." Ed Silverman, *Think Tank Sues FDA for Compassionate Use Documents for an Ebola Drug*, THE WALL STREET JOURNAL (Jun. 10, 2015), http://blogs.wsj.com/pharmalot/2015/06/10/think-tank-sues-fda-for-compassionate-use-documents-for-an-ebola-drug/ (last viewed Mar. 3, 2016). The agency denied the request, saying that release of the information would violate trade secrets. *Id.*

[308] CBSNews, *"Miraculous day": American Ebola patients discharged from Atlanta hospital* (Aug. 21, 2014, 11:12 am), http://www.cbsnews.com/news/ebola-patients-kent-brantly-and-nancy-writebol-discharged-from-hospital/ (last visited Jan. 6, 2015).

[309] *Id.*

[310] Jesse L. Goodman, *Studying "Secret Serums"—Toward Safe, Effective Ebola Treatments*, 371 NEJM 1086, 1087 (2014).

[311] Maggie Fox, *What Cured Ebola Patients Kent Brantly and Nancy Writebol?*, NBC NEWS, August 21, 2014, http://www.nbcnews.com/storyline/ebola-virus-outbreak/what-cured-ebola-patients-kent-brantly-nancy-writebol-n186131. Underscoring Dr. Ribner's point, a Spanish priest and a Liberian doctor who also received ZMapp subsequently died. Donald G. McNeil, Jr., *Liberian Doctor Treated With an Experimental Drug Dies From Ebola*, THE NEW YORK TIMES, 25 August 2014, http://www.nytimes.com/2014/08/26/world/africa/liberian-doctor-treated-with-an-experimental-drug-dies-from-ebola.html.

experimental interventions were extremely limited. For instance, by August 2014, supplies of ZMapp had been exhausted.[312] Given that it was not possible to conduct a valid RCT with so few doses, compassionate use was not necessarily inappropriate, though it still raised questions about fairness in the allocation of a scarce resource, an issue addressed above.

In future public health emergencies, if sufficient doses are available, use should generally be limited to clinical trials. FDA could use its powers to grant or deny EIND requests to steer people away from compassionate use. More importantly, efforts should be made in inter-epidemic periods to assure that sufficient doses are available for clinical research when the opportunity arises. While this is beyond the current powers of FDA, some of the "push" incentives and pre-planning, described above, could be aimed at stockpiling doses for use in future clinical investigations. This is part of making sure that promising drugs are not "stuck" when opportunity knocks.

F. Addressing Repurposing and Off-Label Use of Approved Drugs

As described in Section I, there was interest in the repurposing and off-label prescribing of FDA-approved drugs in the 2014 EVD outbreak because there was a dearth of other treatment options. Repurposing and off-label use hold the potential to address concerns about development, approval, and accessibility and should not be overlooked as vital tools in the effort to combat new and reemerging public health threats. Although they

[312] WHO, *Anecdotal Evidence About Experimental Ebola Therapies*, (Aug. 21, 2014) (http://who.int/mediacentre/news/ebola/21-august-2014/en/) (last visited Mar. 4, 2016).

were not a significant part of FDA's response to EVD, they should be harnessed going forward. I explain why in the next sub-sections.

1. Repurposing

Repurposing is the further development of a drug that is already FDA-approved for a wholly new indication. Repurposing is "a far 'easier lift'" for drug developers than beginning with a wholly new compound because these drugs "have already been subjected to pre-clinical . . . testing and are already deemed to be pharmacologically active, effective and safe in some clinical context."[313] Moreover, results from the clinical trials sometimes indicate that the drug may have effects on similar conditions or viruses transmitted via similar mechanisms. Repurposing speeds development, which hopefully translates to approval and availability sooner than would otherwise be possible. It is thus a means of filling in gaps in our drug arsenal that is beneficial to pharmaceutical companies and consumers alike. How might FDA promote this practice for public health threats?

In 2010, FDA "launched an orphan drug disease development database to encourage manufacturers to develop drugs for rare diseases by identifying products that have already received FDA approval and that have potential to treat rare diseases through added indications."[314] This database, the Rare Disease Repurposing Database (RDRD), is still in

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[313] FDA, *A Valuable Resource for Drug Developers: The Rare Disease Repurposing Database (RDRD)*, http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm (last visited Apr. 14, 2016).

[314] Tim Mackey & Byan A. Liang, *Off-Label Promotion Reform: A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharmaceutical Marketing*, 45 U. MICH. J. L. REFORM 1, 15 (2011).

its Beta version.[315] In future iterations, it should be expanded to include products that have potential to treat NTDs and other public health threats, which may not be rare diseases as statutorily defined in the Orphan Drug Act but need to be addressed nonetheless. Such a database may help with the identification and development of promising compounds during inter-emergency periods, and as has been repeatedly stressed above, would allow for the advanced planning that is needed if clinical research can only be practicably and/or ethically conducted during an outbreak. FDA could also urge companies to move forward with particularly promising compounds, as it has said it will do for rare diseases.[316]

Some have criticized the RDRD because it failed to address the need to incentivize manufacturers to incur the cost of repurposing.[317] Yet, such a database would be complemented by other "push" and "pull" incentives, such as orphan drug designation, PRVs, and fast-track approval.

2. Off-Label Use

FDA does not regulate the practice of medicine, and doctors can prescribe FDA-approved drugs for treatment regimens or patient populations that are not listed in the FDA-approved labeling.[318] It is, therefore, unsurprising that FDA did not vigorously

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[315] FDA, *supra* note 313, at n.p.

[316] Amy Dockser Marcus, FDA Database Aims to Spark Orphan-Disease Drug Development, WALL STREET JOURNAL (Jun. 18, 2010), http://blogs.wsj.com/health/2010/06/18/fda-database-aims-to-spark-orphan-disease-drug-development/ (last visited Apr. 13, 2016).

[317] Mackey & Liang, *supra* note 314, at 15.

[318] *See generally,* FDA, *"Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices - Information Sheet*, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (last viewed Mar. 7, 2016).

address off-label use as part of its response to the 2014 outbreak. In anticipation of future public health emergencies, however, FDA should do more to promote research into off-label uses, and ideally, work to expand product labeling so that safe and effective off-label uses are included in FDA-approved labeling.

Many of the arguments made in Section II in favor of research regarding experimental interventions apply with equal force to off-label uses. Research is important because any given off-label use may not be beneficial and could, in fact, be harmful. Truly novel off label uses are "unlikely to be supported by strong evidence regarding efficacy and safety, even if the drug itself has been on the market for more than 3 to 5 years."[319] In the 2014 EVD outbreak, for example, concerns were specifically raised about the risks of using statins off-label to treat complications of EVD, like organ failure.[320] Elsewhere, I have argued that when an off-label use has a very low certainty of net benefit, it generally should be limited to the context of research protocols.[321] This research does not necessarily need to be conducted by drug companies, and information about off-label uses can be disseminated through medical journals.[322] It is important, at a minimum, that FDA champion such research.

FDA could also consider incentivizing pursuit of FDA approval for a new indication

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[319] Largent, Miller, & Pearson, *supra* note 112, at 1745 (internal citations omitted) (giving the example of Fen-Phen).

[320] *Fast-tracking Treatments: The Hunt for Ebola Medicines is Being Accelerated*, THE ECONOMIST, http://www.economist.com/news/science-and-technology/21616888-hunt-ebola-medicines-being-accelerated-fast-tracking-treatments (last viewed Feb. 29, 2016).

[321] Largent, Miller, & Pearson, *supra* note 112, at 1746.

[322] This implicates a larger literature on publication bias and first amendment issues for off-label promotion, which I will not touch upon here.

on an already approved drug. Adding "additional indications for an already approved medication requires the proprietor to file a supplemental drug application, and, even if eventually approved, revenues for the new indication may not offset the expense and effort of obtaining approval."[323] First, the effective patent life of a drug may be expired or near expiration by the time a manufacturer could benefit from a successful supplemental NDA.[324] Second, a manufacturer is generally able to profit from off-label prescriptions whether or not it pursues a labeling change.[325] If a drug is already off patent, there may be inadequate funding for generic medications to pursue FDA-approval.[326] Thus, "push" and "pull" mechanisms should be considered to allow for the immediate repurposing of existing FDA-drugs while also incentivizing the accretion of socially valuable knowledge.

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FDA's response to the 2014 EVD outbreak highlights the Agency's panoply of powers and demonstrates the flexibility of its regulatory framework. While I have just evaluated FDA's response in terms of its constituent parts and suggested ways in which each could be further strengthened, the overall package of responses must also be

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[323] Christopher M. Wittich, Christopher M. Burkle, & William L. Lanier, *Ten Common Questions (And Their Answers) About Off-Label Drug Use,* 87 MAYO CLIN. PROC. 982, 986 (2012). According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if six conditions are met.

[324] Mitchell Oates, *Facilitating Informed Medical Treatment Through Production And Disclosure of Research Into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1285 (2005).

[325] *Id.*

[326] *Id.*

evaluated in terms of how it met the three overarching goals of drug development, approval, and accessibility. Although some view FDA approval as the bottleneck, this misconstrues the problem. The two biggest problems within the purview of FDA to address are drug development—that is, drugs are not being developed and must pass before clinical trials before FDA can approve them—and post-approval access—once drugs are approved, there is no guarantee they will go where they are most needed. These are the areas in which, viewing the response as a whole, there are the greatest deficiencies and the greatest possibilities for improvement.

Meeting these goals is not the sole responsibility of FDA, and, in fact, I have suggested above that FDA is not always the actor best positioned to address these problems. Nevertheless, it is possible for FDA to work both alone and in concert with others to further each of these ends. Given FDA's stature nationally and internationally, the Agency has the potential to be a powerful advocate for change, and Congressional action could further strengthen its position.

Conclusion

The 2014 Ebola outbreak in West Africa constituted a public health emergency of international concern. FDA was one of the crucial players in the aftermath of the outbreak because there was a need for and emphasis on developing experimental therapies to supplement the current standard of care. As this paper has emphasized, FDA employed a wide swath of the regulatory mechanisms available to it to protect and promote the public health. This entailed collaboration with the medical and scientific community, industry, international organizations, and other regulators. Considering that FDA in meaningful

ways started from behind as the Ebola outbreak unfolded, the end result was a generally effective response. Even now, however, there are no FDA-approved vaccines or drugs for prevention or treatment of Ebola. Moreover, there are concerns about other emerging and re-emerging diseases. The challenges FDA encountered to drug development, approval, and access in the midst of the 2014 outbreak will be encountered continually. Going forward, FDA will have repeated opportunities to take a leadership role in public health emergencies. Lessons drawn from the 2014 outbreak should be used to adapt accordingly.